JOURNAL OF
The American Geriatrics Society

Volume IV *April 1956* Number 4

CONTENTS

The Old and the New in Coronary Artery Disease. *Claude S. Beck* 315

Pulmonary Emphysema Treated with Pneumoperitoneum. *Oscar Neufeld* 328

The Evaluation of Major Surgery for Cancer in the Aged. *Thomas J. Anglem and Martin L. Bradford* 336

Treatment of Cancer with Triethylene Thiophosphoramide and Oxapentamethylene. *Jeanne C. Bateman and Nancy J. Larsen* 341

The Pros and Cons of Estrogen Administration after the Menopause. *E. Kost Shelton* 348

The Rationale of Treating Benign Prostatic Hypertrophy with Combinations of Testosterone and Estrogen. *S. J. Glass* 358

Trends in Research on the Aging Nervous System. *Charles Rupp* 365

Roentgen Therapy of Chronic Chest Symptoms in the Elderly. *Anthony F. Rossitto* 373

Interdisciplinary Research in the Use of Oral Pentylenetetrazol (Metrazol) in the Emotional Disorders of the Aged. Studies in Gerontologic Human Relations. V. *Maurice E. Linden, Douglas Courtney and Allan O. Howland* .. 380

Tube Feeding with Natural Foods in Elderly Patients. *James Barron and Laurence S. Fallis* 400

Abstracts of Current Literature 405

The American Geriatrics Society

Program of the 1956 Annual Meeting 37

The American Therapeutic Society—1955 Annual Meeting 41

Texas Geriatrics Society-Texas Medical Association Meeting (Program) 43

Notice—Bi-Lingual Hebrew Medical Journal 48

Index to Advertisers 50

Entered as second-class matter at the Post Office at Baltimore, Md. Subscription price $10.00 per volume. Published monthly.
No part of any article published in this journal may be duplicated or reproduced without permission of the author, publisher and editor.

JOURNAL OF

The American Geriatrics Society

Official Journal of the American Geriatrics Society

EDITOR IN CHIEF
EDWARD HENDERSON

Editor
PHEBE K. THOMPSON

Associate Editor
FRANCIS M. POTTENGER

Abstract Editor
GLADYS S. KOCH

EDITORIAL BOARD

GEORGE W. AINLAY, SR.
EDWARD B. ALLEN
BROCK E. BRUSH
HOLLIS E. CLOW
WARREN H. COLE
ROBERT ELMAN
FRANK GLENN
GEORGE C. GRIFFITH
NORRIS J. HECKEL
WILLIAM F. HUGHES, JR.
LAURANCE W. KINSELL
WILLIAM B. KOUNTZ
HAROLD W. LOVELL
THOMAS H. MCGAVACK
ROBERT J. PRIEST
CORNELIUS P. RHOADS
LEO T. SAMUELS
HAROLD O. SCHNEIDER
CHARLES T. STONE
RICHARD W. TELINDE
MALFORD W. THEWLIS
MARVIN WEINBERG
MILEY B. WESSON
HAROLD G. WOLFF

Foreign Section

L. BRULL
A. P. THOMPSON

AMERICAN GERIATRICS SOCIETY, Inc.

OFFICERS: *President:* EDWARD HENDERSON, M.D.; *Vice-President:* THOMAS H. MCGAVACK, M.D.; *Secretary:* MALFORD W. THEWLIS, M.D.; *Treasurer:* RICHARD J. KRAEMER, M.D.
BOARD OF DIRECTORS: *Chairman,* MALFORD W. THEWLIS, M.D.; EDWARD B. ALLEN, M.D.; HOLLIS E. CLOW, M.D.; EDWARD HENDERSON, M.D.; RICHARD J. KRAEMER, M.D.
Address of the Secretary: MALFORD W. THEWLIS, M.D., 25 Mechanic Street, Wakefield, Rhode Island.

Subscriptions. The *Journal* is published monthly; twelve issues (Jan.–Dec.) constitute a volume. Subscriptions are sold on a volume basis, prorated if back volumes are not available. The subscription price is $10.00 per volume, plus $.75 per volume postage to foreign countries and the Postal Union, and $.25 per volume to Canada. Subscriptions for members of the American Geriatrics Society are included in the annual dues which are $15.00. Single copies, when available, are $1.25 per copy, plus $.25 postage outside the United States. Publisher must be notified 60 days in advance of change of address. Undeliverable journals will be destroyed.

Correspondence relating to remittances for subscriptions, back volumes and advertising should be sent to THE WILLIAMS & WILKINS CO., Mt. Royal & Guilford Aves., Baltimore 2, Md.

All correspondence concerning editorial matters should be sent to: EDWARD HENDERSON, M.D., 236 Midland Ave., Montclair, N. J.

Correspondence relating to remittances for reprints should be sent to the Waverly Press, Inc., Mt. Royal & Guilford Aves., Baltimore 2, Md.

Correspondence concerning membership applications and membership dues should be sent to: MALFORD W. THEWLIS, M.D., *Secretary,* American Geriatrics Society, 25 Mechanic Street, Wakefield, Rhode Island.

No part of any article published in this journal may be duplicated or reproduced without permission of the author, publisher and editor. COPYRIGHT 1956, BY THE AMERICAN GERIATRICS SOCIETY PRINTED IN U.S.A

JOURNAL OF THE
American Geriatrics Society
Official Journal of the
American Geriatrics Society · American Therapeutic Society · Texas Geriatrics Society

VOLUME IV *April, 1956* NUMBER 4

THE OLD AND THE NEW IN CORONARY ARTERY DISEASE

CLAUDE S. BECK, M.D.*

The Western Reserve University School of Medicine and the University Hospitals, Cleveland, Ohio

A fact in science begins its life history when it is first discovered. Every day marks the beginning of a considerable amount of new scientific information, some of which is of little or no importance. However, history records the discovery of many important facts that were the source of conflict before being accepted by a stubborn and unthinking society. In medicine the physician has not always been on the side of medical progress, because he opposed many advances that subsequently changed the history of medicine. Opposition of this nature is due to the fact that experience establishes patterns of thought and if the experiences are channelled and grooved then the thought is likewise channelled and grooved. No doubt most of us are victims of fixation of thought to a greater or lesser degree, depending upon the breadth and diversity of our experiences.

With these introductory remarks I should like to discuss coronary artery disease—a disease which each year causes a myocardial infarct in 600,000 to 800,000 people and kills over 200,000 people in the United States. This is equivalent to crippling over half of the people in the City of Cleveland and killing everyone in the City of Akron each year. This disease is not just an old man's disease. It strikes in the forties and the fifties when a man is at his best, and when his family needs him most. The cost to society is incalculable. Recently President Eisenhower, speaking of coronary artery disease (before his attack), stated that in war no general could sustain, and society would not tolerate such terrific losses as those caused by this disorder.

The stewardship for patients with coronary artery disease has fallen to the internist, who willingly remains in charge. The internist makes the diagnosis and prescribes rest and sedation. An invisible line separates the electrocardiogram from therapy and the patient is seldom told that there is a difference between the two. The physician finds himself commander-in-chief of the forces arraigned against the most important cause of death, but without effective weapons. He has supreme authority with no commensurate responsiblity. It appears that the

* This work was supported by grants from the United States Public Health Service and the Cleveland Area Heart Society.

physician is often more satisfied with the treatment than is the patient himself. A patient who gets a lot of rest is perplexed when told to get more rest; there is a limit to the amount of rest he can take. The patient seldom understands the fundamental nature of his disease and if he should be told that the medication he has been receiving does not add a single drop of blood to the heart muscle where the blood supply is deficient, he would at least hope for more effective treatment. In a recently published book (1) on myocardial infarction Irving Wright made the following statements: "Coronary occlusion with myocardial infarction presents a formidable challenge to the medical profession. . .treatment was expectant rather than dynamic. . .therapy had not progressed much beyond that used during previous centuries, consisting almost exclusively of rest and sedation." The reason for this unsatisfactory situation is found in the fact that the internist's approach to the study of the disease is channelled and limited by the tools at his command. He is not a surgeon and he does not deal directly with the coronary blood vessels. The situation is comparable to that which existed for mitral stenosis. If the surgeon had not dealt directly with the stenotic valve the treatment of this disease would be back where it was in the hands of the internist. If the internist could deal directly with the coronary vessels, a new era of thought would open up to him and the treatment of the disease would become more effective. A new contribution to this subject has been developed in the experimental laboratory.

WHAT IS THE PROBLEM IN CORONARY ARTERY DISEASE?

In order to solve a problem in science it is necessary that the problem be defined in clear and precise terms. If it cannot be defined, it cannot be solved. The coronary problem can be defined. It concerns the supply of red blood to the heart muscle, but it can be stated with greater precision than this. The problem has two components. One is to provide uniform oxygenation to all parts of the myocardium. The other is to provide sufficient blood to prevent infarction and to supply sufficient energy for the heart beat.

The first part of the definition is illustrated in Figure 1. These hearts illustrate four different conditions of oxygenation in the myocardium and the electrical potentials taken from the heart by direct epicardial leads. A is a uniformly well oxygenated heart; the S-T segment is isoelectric. This heart is electrically stable. C is a uniformly and deeply cyanotic heart; the S-T segment taken from any part of the surface of the heart is isoelectric. This heart is electrically stable. (The heart was made uniformly cyanotic by clamping the intratracheal tube for periods of six to nine minutes. This was performed in 60 dogs by my associate, Dr. David S. Leighninger. In each instance the heart gradually dilated, became deeply cyanotic, and finally came to a standstill. In no experiment did the heart fibrillate. When oxygen was again delivered into the lungs and the heart was emptied a few times by manual squeezing, a normal coordinated beat was restored. Thus the heart changed from pink to blue, to pink again, without the development of electrical potentials that destroyed the mechanism). B and D are electrically unstable hearts. B is a pink heart, as in A, except that the de-

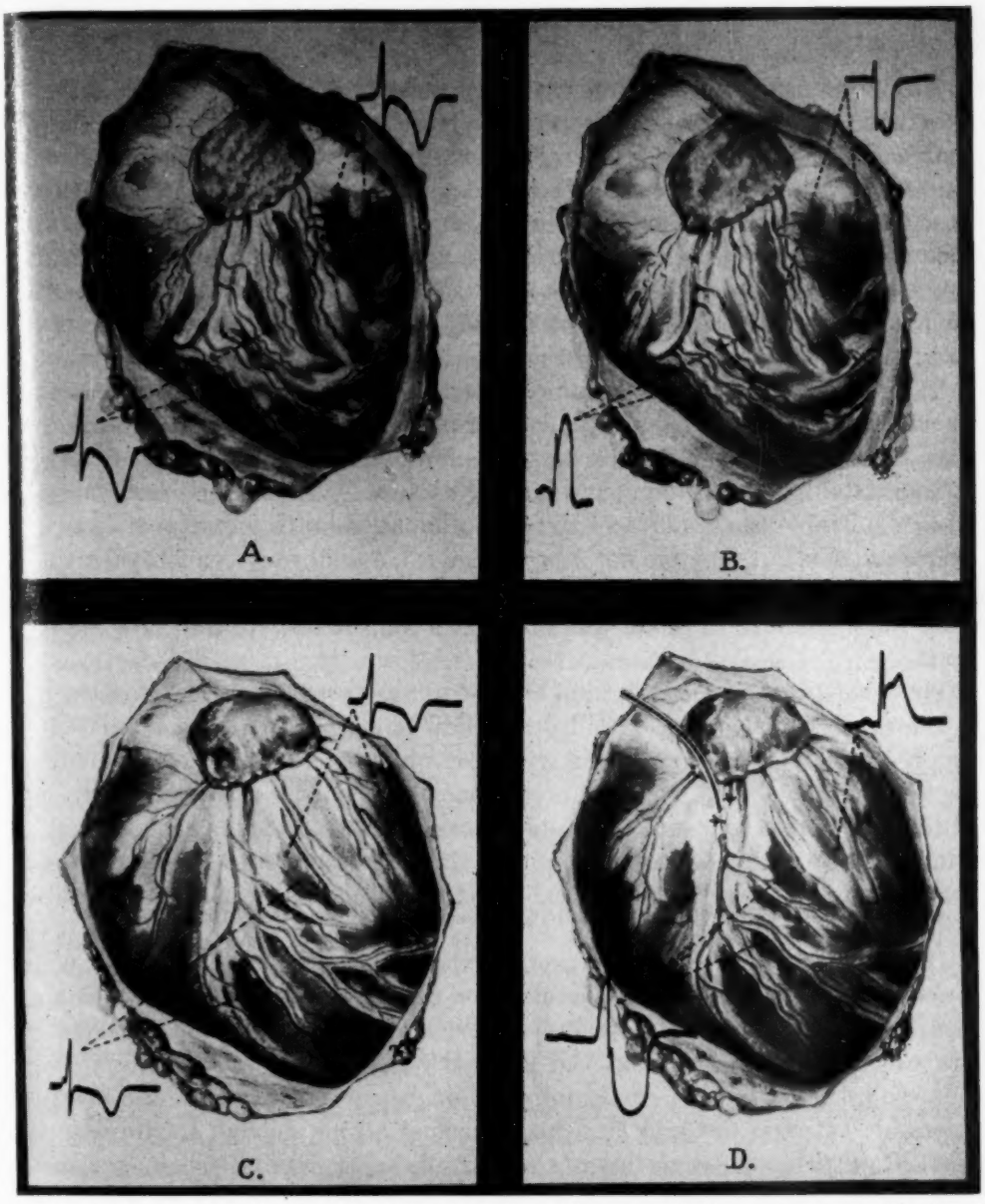

FIG. 1. Dog hearts illustrating four conditions of myocardial oxygenation, with direct epicardial electrocardiograms demonstrating measurement of electrical potentials. **A** and **C** are the same heart; the one is uniformly well-oxygenated and the other is uniformly and severely cyanotic. These hearts are electrically stable, as shown by the isoelectric S-T segment in each condition. **B** and **D** are electrically unstable, because the oxygen tension in each heart is not uniform throughout. **C** is a well-oxygenated heart everywhere except for the area supplied by the descending ramus of the left coronary artery, which is ligated; the ligature can be seen on the artery. This produces a cyanotic area of muscle supplied by the artery. **D** is a cyanotic heart, as shown in **C**, except that a cannula is placed in the descending coronary artery and oxygenated blood is perfused into the muscle supplied by this artery. This produces a pink area in a blue heart. The S-T segment is depressed over the pink or well-oxygenated myocardium and elevated over the blue or cyanotic myocardium. These differences in potentials are often strong enough to fibrillate the heart. The term "current of oxygen-differentials" is introduced to replace "current of injury," which is obviously incorrect. A uniformly cyanotic heart is not an injured heart. (Courtesy of *J.A.M.A.* (9).)

scending ramus of the left coronary artery is ligated (the ligature can be seen). The muscle beyond the ligature becomes blue, so that a blue island exists in a pink heart. D is a cyanotic heart, as in C, except that the descending ramus of the left coronary artery is cannulated and oxygenated blood is perfused into this artery, so that a pink island exists in a blue heart. The zone of contact between blue and pink, and pink and blue shows differences in electrical potentials. The S-T segment is depressed over the pink areas and elevated over the cyanotic areas. These differences in potentials may be strong enough to fibrillate the heart and destroy the coordinated mechanism.

In the past the currents obtained after ligation of a coronary artery were referred to as currents of injury. This term is not correct, because a uniformly cyanotic heart is not an injured heart. We propose the term "current of oxygen differentials" instead of current of injury. A blue baby does not have an electrically unstable heart, nor does the cyanotic patient with valvular disease. The hearts are blue but they are not injured. Indeed, a uniformly cyanotic heart may be more stable than a uniformly pink heart, because it requires more current from the outside to fibrillate the blue heart than it does to fibrillate the pink heart.

The second part of the definition of the coronary problem involves destruction of the myocardium and the ability to pump blood. As in the first part, blood supply is involved, but in an entirely different manner because the heart remains electrically stable from one bout of coronary occlusion to another and the currents which are a side-effect of muscle destruction are not strong enough to fibrillate the heart. Repeated occlusions are withstood until finally the heart muscle gives away in failure, or the blood supply is inadequate and the heart stops beating.

This definition of the coronary problem throws new light on the subject, which is now open to logical attack. The problem is not entirely one of blood supply. The man who falls over dead while shoveling snow has enough total blood getting into the myocardium; in fact the exercise oxygenates the myocardium very well, except in one area where the lumen of an artery is reduced and the electrical potentials between the pink and blue becomes strong enough to fibrillate the heart. Had this man sat on the sofa indoors his heart would not have become so pink, the oxygen differentials would not have been so marked, and the probability is he would not have died.

This definition involves radical changes in medical thought concerning coronary artery disease. It indicates that oxygen, or the lack of it, has two different effects upon the heart. *Differences* in oxygen content in adjacent areas of myocardium produce electrical potentials that are dangerous. Such differences in oxygen content are not to be confused with *lack* of oxygen, because the uniformly cyanotic heart has little oxygen but no differences in electrical potentials. Up to the point of stoppage of the heart it is just as stable or even more so than the uniformly pink heart. These differences in electrical potentials are not related to infarction or death of muscle and they often kill without an infarct. While an infarct is developing, differences in potentials may or may not be strong enough to fibrillate the heart. These currents may be under the threshold of that causing

fibrillation, so that the beat is maintained from one infarct to another as the arterial disease progresses, and finally the condition is one of heart failure.

Another point brought out by this definition concerns the disease process in the coronary arteries. The question has been raised as to whether the experimental work on the coronary arteries is valid, because coronary arteriosclerosis cannot be induced in dogs. The answer to this question is obvious. The arterial disease reduces blood flow. This is a side-effect of the arteriosclerotic process but it is the factor that kills the patient. In the experimental work the blood supply was reduced by ligation of one or more coronary arteries. Even if the arteriosclerotic process could be produced experimentally it would not be a satisfactory method for scientific study because the degree of occlusion and the site of the occlusion could not be regulated with any degree of precision. As a method for reduction of blood flow, ligation is preferable to the disease for purposes of scientific studies.

REVERSIBLE DEATH IN CORONARY ARTERY DISEASE—GIVING THE HEART A SECOND CHANCE TO BEAT (2)

At 11:30 A.M. June 22, 1955, a 65-year-old physician had an electrocardiogram made at University Hospitals. He had precordial pain while the record was being obtained and the interpretation of the electrocardiogram by Dr. Harold Feil was as follows: "This is an abnormal record showing S-T elevation in 2, 3, AVF, and V6 consistent with ischemia of the posterolateral wall and the anginal pain which the patient was experiencing at the time the record was taken." The patient was advised to go home and rest. On the way out of the hospital he fell to the floor. He was placed on a wheel cart by Drs. Elton Weckesser and Frank Barry and hurriedly transported to the accident room, which was nearby. No pulse or heart sounds were present. The patient was cyanotic and dead. The left chest was slit open, an intratracheal tube was inserted, and the lungs were inflated. The heart was emptied by hand massage; it was fibrillating. Large electrodes were placed on the heart and it was shocked several times. Adrenalin (1 cc. of 1–1000, diluted with 10 cc of saline) was injected into the cavity of the heart. The oxygen system was maintained by hand and twenty-five minutes went by. I was called and on arrival found that everything was in order. The incision was enlarged slightly to give more room for the surgeon's wrist and the lungs were better inflated and deflated. I knew the crisis was over and time was taken to put on gloves and a gown and to bring sterile linen into the field. I then opened the pericardium and found coarse ventricular fibrillation. The heart had good tone and wanted to beat. Two shocks were given but the electrodes were dry and the full current did not penetrate the heart. Then the electrodes were wet with saline and the next shock was effective. A normal coordinated rhythm was restored. The blood pressure was 120 mm. of Hg and the pulse rate was 86 per minute. Beads of perspiration appeared on the dead man's forehead as life was restored. The rest of the patient's clothes were removed and his shoes were taken off. At 4:00 P.M. of the same day an electrocardiogram was taken and the report was: "Since the record of earlier today, an acute posterior myocardial infarct has appeared. Digitalis effect is now present." Cedalanid was given during the procedure. The patient was confused and disoriented for two days and then returned to normal. Subsequent records showed evolution of an acute posterior infarct and pericarditis. A mild wound infection developed, involving a costal cartilage. The patient rested at home. As of August 1, 1955 he felt tired but was able to resume his practice of medicine.

Electrical potentials in this case were strong enough to fibrillate the heart and kill the patient. This occurred even though the heart was still strong enough to beat. On the basis of the record the heart needed a *second chance* to beat. The

following question has been raised by several internists: "If you knew this man had coronary artery disease you would not have tried to resuscitate him, would you?" The answer is given by the fact that the man is alive, and that the resuscitation procedure changed the status from death to life. This query indicates that the internists who asked this question do not understand the problem in coronary artery disease. The problem is to protect the heart from the development of electrical potentials—a condition that kills so many people each year whose hearts are capable of continued function. Protection can be provided by surgical operation and it must be provided early before the electrical currents become strong enough to fibrillate the heart and before extensive damage occurs in the heart muscle.

TWO TYPES OF DEATH

This definition of the coronary problem lays the subject open to scientific study and future progress. It implies that there are two types of death in coronary artery disease. One is due to break in the coordinated mechanism, and the other is due to muscle damage. One occurs in hearts in which the electrical potentials become strong enough to cause fibrillation, and the other occurs in hearts which remain electrically stable while the arterial disease causes one infarct after another and damages enough muscle to induce failure. The group of patients who die from failure constitute about 10 per cent of the entire number (3). The remaining 90 per cent die from electrical instability. The dividing line between these two groups is not sharp, because the heart in failure may show development of instability and fibrillation, or the heart that fibrillates may be approaching the status of failure. However, this division into two groups serves a useful purpose in the understanding of the coronary problem. About one third of all victims of coronary artery disease have no infarct, either old or recent (4); the remainder die of electrical instability in the presence of an infarct. Many of these hearts could

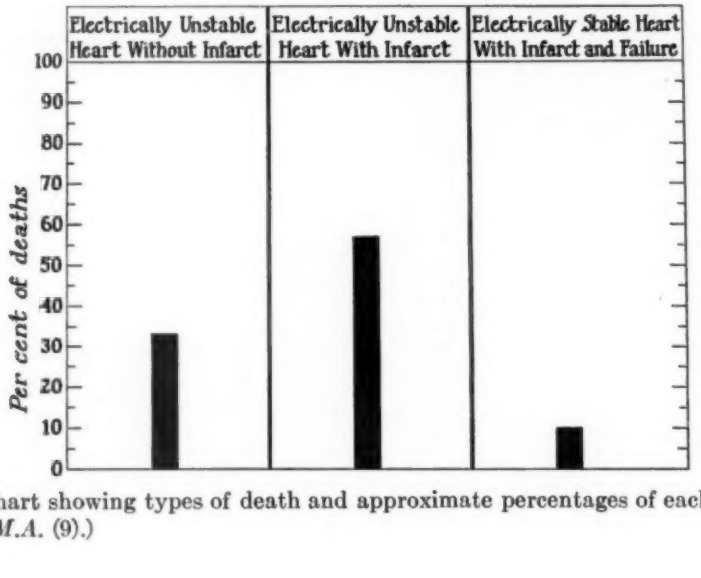

FIG. 2. Chart showing types of death and approximate percentages of each type. (Courtesy of *J.A.M.A.* (9).)

keep on beating under slightly improved circulatory conditions or, as in the case here referred to, could continue to beat even though the circulatory conditions are not improved. In our patient the heart needed a second chance to beat. Figure 2 shows the percentages of deaths in each of these groups.

METHODS FOR IMPROVING A CRIPPLED CORONARY CIRCULATION

In general, there are two methods for improving the coronary circulation. These are 1) by establishing an equal distribution of the blood that enters the heart through the constricted arteries, and 2) by the addition of blood from sources outside the heart. These two methods do not include possibilities in the future of plastic operations on the diseased arteries, such as resection of a segment of vessel with placement of a graft, the production of a shunt between a systemic source of blood and a coronary artery, or performance of an endarterectomy. These possibilities require a non-beating heart and present problems that cannot be discussed here.

At the present time the most effective method is by the establishment of intercoronary arterial communications. Such peripheral communications between descending ramus, circumflex ramus, and right coronary artery would make it possible for a red blood cell after it enters one of the arteries to move from one vascular bed to another. Thus if artery A were blocked off, then through these communications blood could enter the myocardium normally supplied by A, from arteries B and C; and if both A and B were blocked off, the vascular beds of these occluded arteries could be supplied by artery C alone. Indeed, autopsy specimens show that the heart can beat when it is supplied by only one artery, or even by a small part of one artery. Hahn and I succeeded in producing almost but not quite complete occlusion of all coronary arteries in dogs (5). Complete occlusion of all arteries has been reported in human hearts. Total coronary inflow is a factor in coronary disease, especially in the 10 per cent of patients in whom failure develops; but distribution is a much more important factor, because uneven distribution accounts for 90 per cent of all deaths from this disease.

A stimulus for the production of intercoronary arterial communications is coronary artery occlusion plus time. When an artery is occluded the pressure beyond the occlusion falls and the myocardium becomes anoxic. Both of these states may be factors in the production of intercoronary channels and, in my opinion, the pressure differential is more effective than the anoxia. A second stimulus for the production of such intercommunications is inflammation, whether caused mechanically or chemically. We have found that these channels may be produced by abrasion of the epicardium and parietal pericardium (6). Of many chemical agents tested we found that asbestos was the most effective and stimulated the most satisfactory reaction. Necrotizing chemicals such as carbolic acid should not be used on the heart. Ligation of the coronary sinus also aids the coronary artery system if an artery is occluded. Sinus ligation does not aid a normally patent system of coronary arteries, because the resultant increased pressure in the veins and capillaries reduces coronary artery inflow;

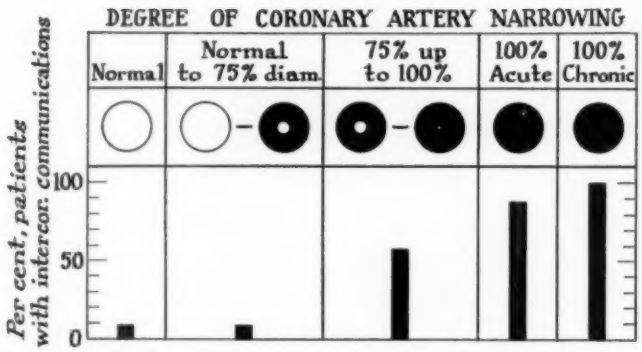

FIG. 3. The incidence of intercoronary arterial communications in the normal human heart and in hearts showing different degrees of coronary artery occlusion—based upon studies by Zoll, Wessler, and Schlesinger (7).

but if a coronary artery is occluded, ligation is beneficial. It is effective in three ways: 1) by more complete extraction of oxygen from the blood, 2) by venous engorgement, which reduces oxygen differentials when an artery is occluded, and 3) by the production of intercoronary channels. Zoll, Wessler and Schlesinger have studied intercoronary channels in 1,050 human hearts (7). They reported the presence of anastomoses in cor pulmonale, cardiac hypertrophy and valvular lesions, and in normal hearts from patients with anemia, and suggested that in all these conditions cardiac anoxia is the underlying stimulus for development. These authors made a study of coronary artery occlusion in relation to intercoronary communications, which they found to be present in 9 per cent of normal hearts. This percentage did not change until the occlusive process reached 75 per cent of the diameter of an artery. Thus the incidence was 9 per cent in occlusive disease up to the level of marked occlusion of an artery. The incidence rose to 58 per cent when the occlusive disease was between three-fourths and not quite complete occlusion. In the presence of complete occlusion the incidence was 89 per cent when the occlusion was acute, and 100 per cent when it was chronic (Fig. 3).

These studies by the Boston investigators are important from the standpoint of surgical operation for coronary artery disease. In the first place they showed that only 9 per cent of normal human hearts have these channels and the persons concerned are probably born with them. No doubt these are the individuals who could survive a coronary artery occlusion and live for fifteen years without symptoms. The cardiologist is always enthusiastic about such star performances because they are so good and also because they are unusual—only about 9 per cent of people have these channels. The purpose of surgical operation in the treatment of coronary artery disease is to give the remaining 91 per cent of the people a set of intercoronary vessels as good or better than those of people who are born with them. In normal dogs the incidence of intercoronary channels also varies. In 65 normal dogs my associate, David Leighninger, showed that the number of these channels was below average in 68 per cent and above average in 32 per cent. In 6 of these dogs they were well developed. In 40 dogs in which the

Number 1 operation was performed, the number of intercoronary communications was below average in 20 per cent and above average in 80 per cent. The second point brought out by the Boston study concerns the effectiveness of stenosis as a stimulus. The stenotic process does not become effective until it involves 75 per cent of the diameter of an artery. It is unfortunate that lesser degrees of narrowing are ineffective in producing intercoronary channels, because the narrowing gives rise to electrical instability of the heart and such channels would reduce the oxygen differentials. This in turn would save life in a large group of people who die with a good myocardium. Even with narrowing from 75 per cent up to, but not including occlusion, the incidence rises only from 9 per cent to 58 per cent. Forty-two per cent of these patients do not have the protection of intercoronary communications, and in these people with severe narrowing arise the differences in electrical potentials which kill. With occlusion, the incidence increases to 89 or 100 per cent. With acute occlusion, 11 per cent of patients die because coronary intercommunications are not present; once the acute process of narrowing becomes complete in this group the beat is lost. All patients with chronic occlusions have these channels. It should be emphasized that the presence of intercoronary communications keeps the heart beating so that the occlusive process has time to become complete and chronic. It is not the other way around—that chronic occlusion produces the communications. These patients in the 100 per cent group might well be those represented in the first column of Figure 3. The desirability of producing intercoronary channels is obvious, especially in patients such as those in columns 2 and 3, in whom the incidence is so low. It is unfortunate that coronary stenosis is not a more effective stimulus for their production. It may be that these *ineffective degrees of stenosis when added to the stimulus of inflammation* may become effective. This subject is being investigated.

Intercoronary channels aid in the even distribution of blood after an artery is occluded. They do not bring additional blood to the heart. We have investigated some possibilities of adding blood to the heart. One of these was by grafting tissues onto the heart, with the expectation that blood vessels would develop between the graft and the heart. The tissues used were parietal pericardium, mediastinal fat, chest wall, substernal muscle with internal mammary arteries, lung, omentum, bowel, and spleen. In general, these grafting operations protected the heart against occlusion, because the operation caused enough inflammation on the surface of the heart to give rise to intercoronary communications. In an occasional specimen it was possible to demonstrate vessels between the graft and the heart that were large enough to carry blood, but no flow measurements were made in these experiments.

The other possibility for adding blood was to convert the coronary sinus into an artery, with the expectation that blood would flow in a retrograde direction. This operation was one of the most difficult technical developments in surgery. It was accomplished in two stages. The first stage consisted of tapping the aorta for blood by placing a free vein graft between the aorta and the coronary sinus. This formed an arteriovenous fistula. Two or three weeks later the coronary

sinus was ligated to a diameter of 3 mm. and the ligature was placed where the sinus entered the right auricle. This reduced the amount of blood in the fistula and increased the flow into the muscle. Blood actually traversed the capillary bed from the graft for the first six weeks after the second stage of the operation was performed. Then intimal thickening of the veins occurred and, thereafter, blood did not go in a retrograde direction. However, the operation protected the heart by producing an excellent set of intercoronary channels, and these were permanent. This two-stage operation has been labeled the No. 2 operation and will not be discussed here (8).

THE BECK I OPERATION (9)

This operation consists of the following procedures—abrasion of the lining of the parietal pericardium and the surface of the heart, partial ligation of the coronary sinus to a diameter of 3 mm., the application of an inflammatory agent to the surface of the heart (0.2 to 0.4 Gm. of coarsely ground asbestos), and grafting of mediastinal fat and parietal pericardium to the surface of the heart. Each component of this operation contributes something to the total protection, and each has been measured individually, as shown in Figures 4 and 5. One fundamental measurement after another has been published and these will be referred to only briefly. When this operation was carried out on a large number of dogs and then at some subsequent time the descending ramus of the left coronary artery was ligated, the dogs which had had the protective operation died at the rate of 26.6 per cent, whereas in normal unprotected dogs the mortality following

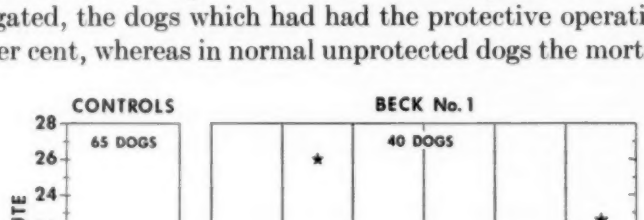

FIG. 4. Mautz-Gregg backflow in normal dogs and in dogs in which the No. 1 operation had been performed. Protection was present at 12 months. Once this protection is established it is probably permanent. Dogs marked by a star showed protection in the electrocardiogram after the circumflex artery was ligated. (Courtesy of *J.A.M.A.* (9).)

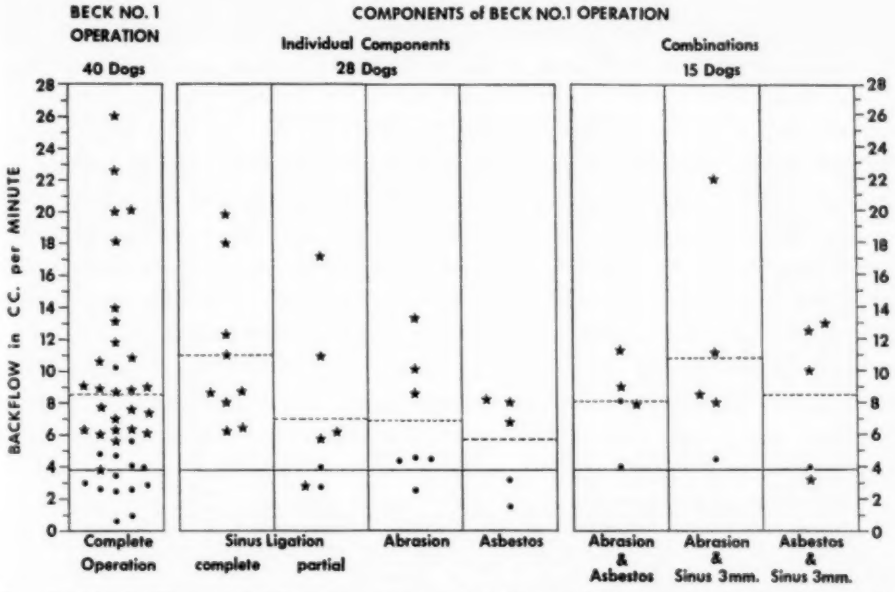

FIG. 5. Mautz-Gregg backflow measurements in dogs which the No. 1 operation had been performed and also in dogs in which various components of the operation had been performed. Each component provided protection. Dogs marked by a star showed protection in the electrocardiogram after the circumflex artery was ligated. (Courtesy of *J.A.M.A.* (9).)

ligation of this test artery was 70 per cent. This indicated that the heart was electrically stabilized by the operation. The infarct in the dogs that recovered was 60 to 70 per cent smaller in the protected group than it was in the normal control dogs. In many of the protected hearts there was no gross infarct but an infarct was always found in the normal control group. Therefore, the operation reduced the process of infarction after coronary artery occlusion. The electrocardiogram showed fewer and less severe abnormalities following test artery ligation in the protected group than in the normal dogs. Mautz-Gregg backflow studies were made by Leighninger. This method of study is an important adjunct in such work because it provides the explanation for the protection. The process is as follows—the circumflex ramus of the left coronary artery is dissected out at its origin, ligated proximally, and cut across at a point distal to the ligature; the distal end is cannulated and the amount of blood from the artery is the backflow. The backflow comes from the descending ramus and from the right coronary arteries; part of it may come from vessels in tissues grafted on the heart. In 65 normal dogs the average backflow was 3.8 cc. per minute. After the No. 1 operation was performed, and for a period thereafter, the backflow was measured; the average in 40 dogs was 8.5 cc. per minute. This means that the operation increased backflow by 4.7 cc. per minute (8.5–3.8), or 282 cc. per hour. This is equivalent to a transfusion of 282 cc. of red blood per hour to the circumflex area of the myocardium after it has been made ischemic by circumflex ligation. Furthermore, the blood is there immediately after the artery is ligated. Thus, blood is present and available to help carry the dog or the human over the

crisis of an acute and total occlusion. Such a weapon to meet this crisis the internist does not possess.

LIMITATIONS OF TREATMENT

Prevention of the sclerotic process in the arteries is the ultimate goal, but until this can be accomplished the nature of the therapy is of paramount importance. Medical and surgical methods of treatment have positive values but each also has limitations, and in order to appraise these values it is necessary to understand the limitations. No method of treatment will stop the occlusive disease or restore degenerated myocardium. The effectiveness of any form of treatment becomes progressively reduced as the myocardial degeneration advances to the stage of failure. The disease process may become more severe or fatal at any time, regardless of treatment. Our definition of the coronary problem clearly points to the two aspects of the disease. The dominant one concerns oxygen differentials, electrical potentials and fibrillation. The amount of work by the heart and the emotional expenditures by the patient influence these potentials. Thus rest, sedation and reduction of work load are important therapeutic measures. Various drugs reduce pain but the mechanism by which this is accomplished is not established. The role of intercoronary arterial communications is of great importance. There is no evidence that any medication can stimulate their formation, but there is scientific proof that surgical operation can do so. There is also evidence that surgical operation can add blood to the heart from outside sources, but this evidence is incomplete. Coronary artery occlusion, following either disease or ligature, can result in intercoronary communications, but stenosis is not always an effective stimulus. Production of inflammation on the heart is more effective, and it is probable that these two stimuli together have an augmented effect. The results of operation on patients with coronary artery disease appear to be better than expected on the basis of the experimental measurements. In dogs the operations were performed on normal major coronary arteries which were suddenly completely occluded but in the human the operation is performed on arteries already occluded by disease. It is probable that inflammation brought about by operation has an augmented effect on the production of intercoronary communications if ineffective pressure differentials from the disease are present when the operation is performed.

APPLICATION TO PATIENTS

Up to the time of writing (August 1955) approximately 300 patients with coronary artery disease have been operated upon by me. The first operation was performed in 1935. The early technique was the No. 1 procedure, with the exception of partial ligation of the coronary sinus, which was not used. The two-stage operation was developed in the 1945–1954 period and was applied to patients. From January 1, 1954 to the present the No. 1 operation has been used. A discussion of the two procedures has been published (8, 9).

The diagnosis of coronary artery disease was well established in all patients accepted for operation. The great majority had one or more infarcts. We learned not to accept patients with failure, dyspnea, and marked enlargement of the

heart. Acceptance of such cases increased the mortality rate and it is questionable whether operation could be beneficial in the presence of extensive irreversible damage to the myocardium.

Patients with slight to moderate enlargement of the heart are accepted, but extensive damage is sometimes found at operation. These are classified as a salvage group and I am always doubtful as to whether the operation can possibly help them. However, some of the best clinical results are obtained in patients with severe damage, despite the fact that the best results should be obtained in those with localized ischemia and without extensive damage in the heart. Nine out of 10 patients are helped by operation. They are either partially or completely relieved of pain, and can return to work. It is almost necessary to see these people to appreciate and accept these results. In the last 100 operations the mortality was 6 to 8 per cent (2 deaths were from thoracotomy alone). Most of these patients had severe disease and the mortality was due primarily to the disease and secondarily to the operation. The mortality can be raised or lowered by selection of cases. The present level covers acceptance for operation of patients with extensive disease.

SUMMARY AND CONCLUSIONS

1. The problem of coronary artery disease is defined, thus opening the subject to scientific understanding and attack.

2. Surgical operation protects the heart and relieves the symptoms caused by coronary arteriosclerosis. These results are brought about because the operation produces intercoronary arterial channels.

3. Clinical results of the operation are presented.

REFERENCES

1. Wright, I. S.; Marple, C. D., and Beck, D. F.: Myocardial Infarction. Its Clinical Manifestations and Treatment with Anticoagulants. New York, Grune & Stratton, 1954.
2. Weckesser, E. C.; Barry, F. M., and Beck, C. S.: Reversible death in coronary artery disease, *J.A.M.A.* (in press.)
3. Yater, W. M.; Beck, C. S.; Leighninger, D. S., and Brofman, B. L.: Symposium on coronary arterial disease, *Am. Rev. Tuberc. & Pulm. Dis.* **71:** 904 (June) 1955.
4. Yater, W. M.: Coronary artery disease, *Med. Ann. Distr. Columbia* **20:** 313 (June) 1951.
5. Hahn, R. S., and Beck, C. S.: Revascularization of the heart: a study of mortality and infarcts following multiple coronary artery ligation, *Circulation* **5:** 801 (June) 1952.
6. Schildt, P.; Stanton, E., and Beck, C. S.: Communications between the coronary arteries produced by the application of inflammatory agents to the surface of the heart, *Ann. Surg.* **118:** 34 (July) 1943.
   Stanton, E.; Schildt, P., and Beck, C. S.: The effect of abrasion of the surface of the heart upon intercoronary communications, *Am. Heart J.* **22:** 529 (Oct.) 1941.
   Beck, C. S.: The development of a new blood supply to the heart by operation, *Ann. Surg.* **102:** 801 (Nov.) 1935.
7. Zoll, P. M.; Wessler, S., and Schlesinger, M. J.: Interarterial coronary anastomosis in the human heart, with particular reference to anemia and relative cardiac anoxia, *Circulation* **4:** 797 (Dec.) 1951.
8. Beck, C. S., and Leighninger, D. S.: Operations for coronary artery disease, *J.A.M.A.* **156:** 1226 (Nov. 27) 1954.
9. Beck, C. S., and Leighninger, D. S.: Scientific basis for the surgical treatment of coronary artery disease, *J.A.M.A.* **159:** 1264 (Nov. 26) 1955.

PULMONARY EMPHYSEMA TREATED WITH PNEUMOPERITONEUM

OSCAR NEUFELD, M.D.*

Toledo, Ohio

The attitude of the medical profession toward pulmonary emphysema is sometimes prone to be one of pessimism. Few realize that severe forms of pulmonary emphysema occur frequently in young and middle-aged persons. Too little attention has been drawn to the early stages of the disease when it may be completely reversible. Pulmonary emphysema is a common, disabling, and chronically progressive disease occurring as a complication of practically all pulmonary diseases. Early recognition and prompt therapy are needed to prevent permanent disability. Diagnosis is not particularly difficult, but therapy heretofore generally has been inadequate.

Encouraging results have been obtained with the use of pneumoperitoneum. In severe pulmonary emphysema, the state of chronic hyperinflation of the lungs necessitates increased muscular exertion during expiration and makes it impossible to empty the lungs to a normal extent. Diaphragmatic function is impaired and the breathing reserve is reduced, laying the foundation for dyspnea. Pneumoperitoneum is of particular benefit in improving the capacity for diaphragmatic breathing.

Reich (1), in 1924, was the first to introduce artificial pneumoperitoneum in the treatment of pulmonary emphysema. He emphasized that one of the chief complaints of the patient was difficulty in expelling air. He observed, following the injection of air, elevation of the diaphragm with increased excursion, reduction in dyspnea, and subjective improvement.

Duomarco, Rimini and Recarte (2) demonstrated a close relationship between intrapleural and intra-abdominal pressure in patients with uncomplicated emphysema. The intraperitoneal injection of air causes the diaphragm to rise toward the lungs, reducing thoracic capacity and restoring the normal negativity of the intrapleural pressure. This permits greater contraction of the elastic structures of the lung and relaxation of pulmonary tissue and peribronchial smooth muscles. Lung volume is reduced, and the diaphragm can again function as an important respiratory muscle. Improved expectoration removes inflammatory exudate from the lower air passages, so that there is greater accessibility of the alveoli for inspired air.

The results reported by Carter, Gaensler and Kyllonen (3) were an increase in vital capacity, decrease in residual air, increase in maximum breathing capacity, and reduction in minute ventilation. The decrease in the volume of residual air implies more adequate diffusion of gases in the lungs. Minimization of anoxia decreases the likelihood that pulmonary hypertension, dilatation of the pulmonary artery, or hypertrophy of the right ventricle will develop.

* F.C.C.P. Address: 237 Michigan Avenue, Toledo, Ohio.

Pneumoperitoneum, however, has definite limitations. Heart failure that cannot be corrected, atrophy of the diaphragm, diaphragmatic adhesions, widespread pulmonary fibrosis, and irremediable loss of alveoli are the causes of failure. Patients to be treated with pneumoperitoneum must be carefully selected.

The following study shows the effects of treatment with pneumoperitoneum on patients with severe pulmonary emphysema but with no definite evidence of heart failure.

PRESENT STUDY

Fourteen patients from 46 to 63 years of age were selected for a study of the effects of artificial pneumoperitoneum. All had far-advanced pulmonary emphysema with chronic bronchial infection. The following criteria determined the

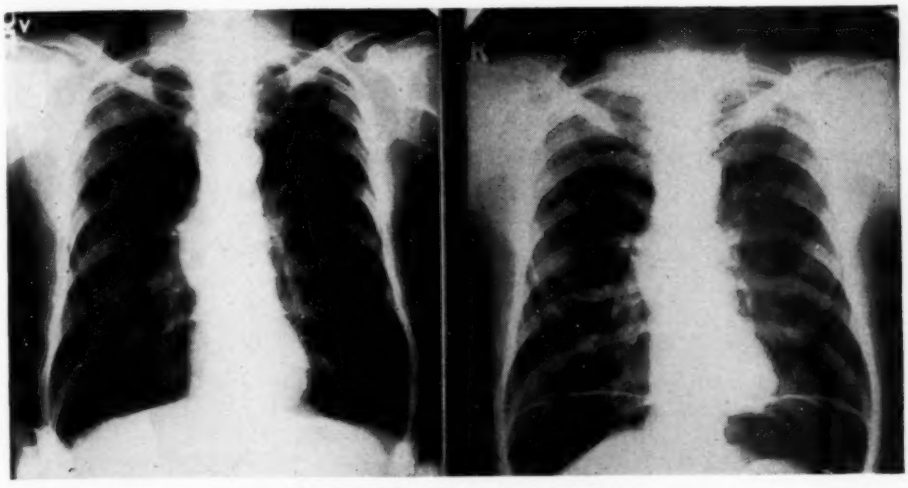

FIG. 1. Patient 8, after one day.

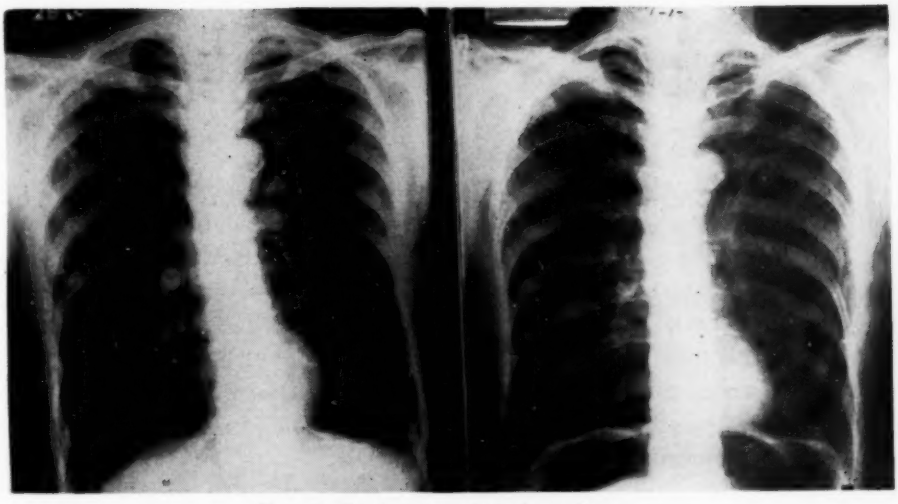

FIG. 2. Patient 4, after four days.

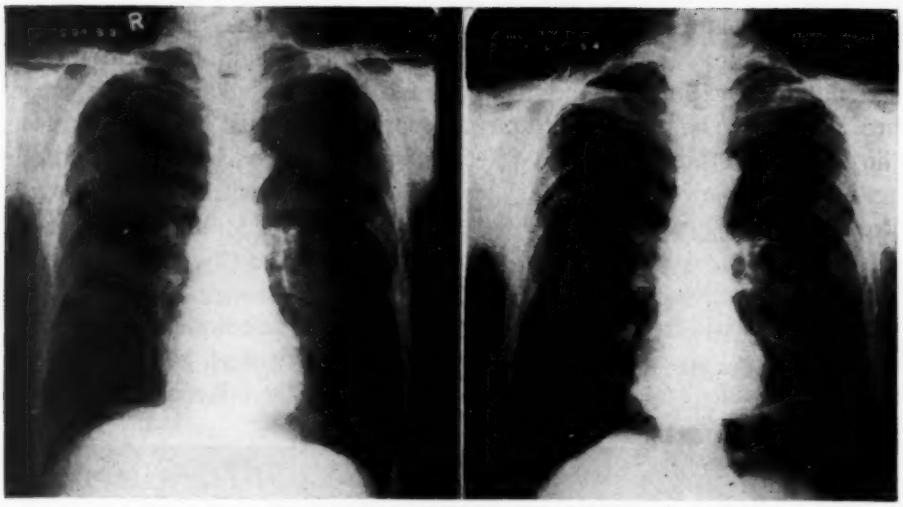

FIG. 3. **Patient 1, after one day.**

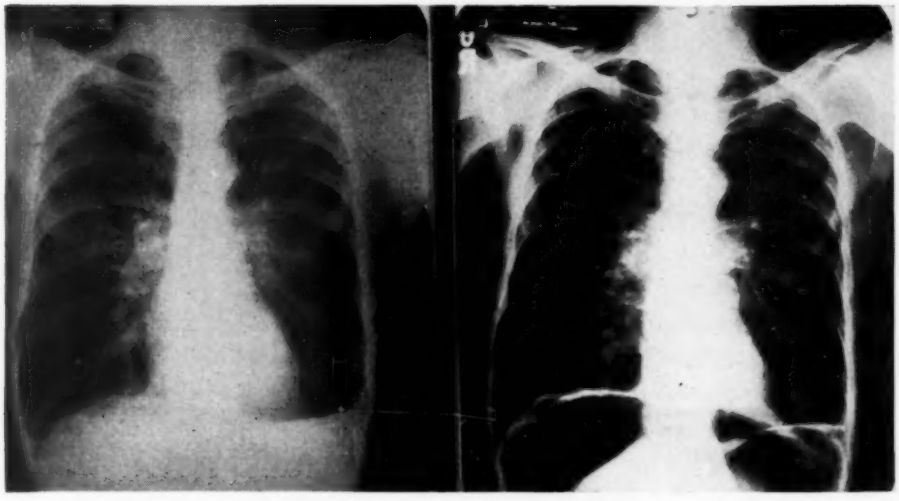

FIG. 4. **Patient 3, after two days.**

selection of patients: the presence of pulmonary insufficiency with dyspnea to an extent incapacitating for work; cor pulmonale, minimal, if present; pulmonary infection controlled; and the absence of tuberculosis, tumors, obstruction and severe bronchiectasis, established by means of bronchoscopy and other studies.

Dyspnea was the most marked symptom. In Table 1, which summarizes the clinical data, dyspnea is graded 4 plus for patients with severe restrictions, in respiratory distress, and unable to work. The next most distressing symptoms were cough and the presence of sputum. Rales, rhonchi and wheezes also were present in all the patients.

The temperatures and pulse rates of all the patients were normal at the onset of pneumoperitoneum. Blood pressure determinations ranged from 120/80 to 152/106. Venous blood pressure readings were from 30 to 60. Hemoglobin con-

centrations were from 10 to 14.5 Gm., and hematocrit values were from 38 to 50. Bronchoscopic examination revealed inflammatory changes in the bronchial mucosa in 9 patients having partial bronchial obstruction; the findings were negative in 5 patients. Electrocardiograms were normal in 11 patients, showed right axis deviation in 2, and myocardial damage in 1.

Thirteen of the 14 patients spontaneously reported improvement as a result of pneumoperitoneum therapy; 1 showed no improvement. Reduction in dyspnea and in cough, ability to raise secretions easily, and increased tolerance for exercise characterized the subjective improvement noted. Improvement usually was maximal for four to five weeks after the induction of pneumoperitoneum. Fluoroscopic examination showed that the average range of diaphragmatic motion was 40 per cent of normal, in contrast to 10 per cent of normal prior to treatment.

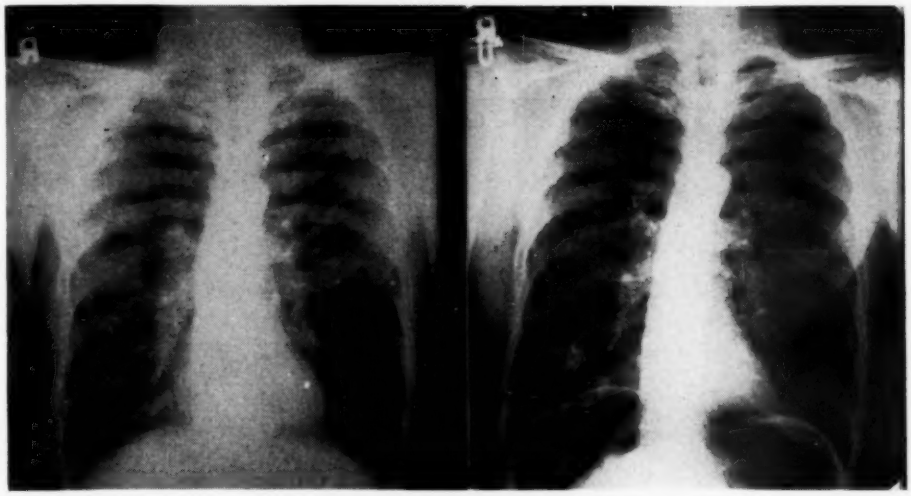

FIG. 5. Patient 2, after two days.

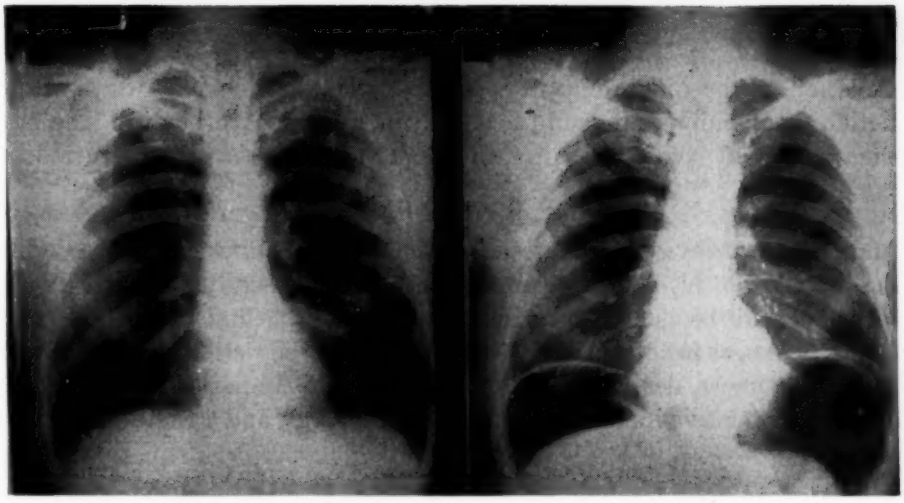

FIG. 6. Patient 6, after ten days.

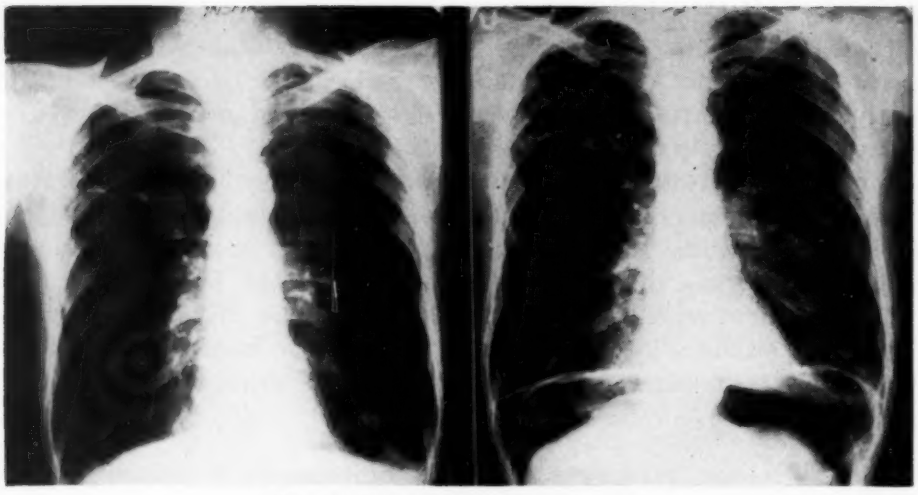

FIG. 7. Patient 10, after one day.

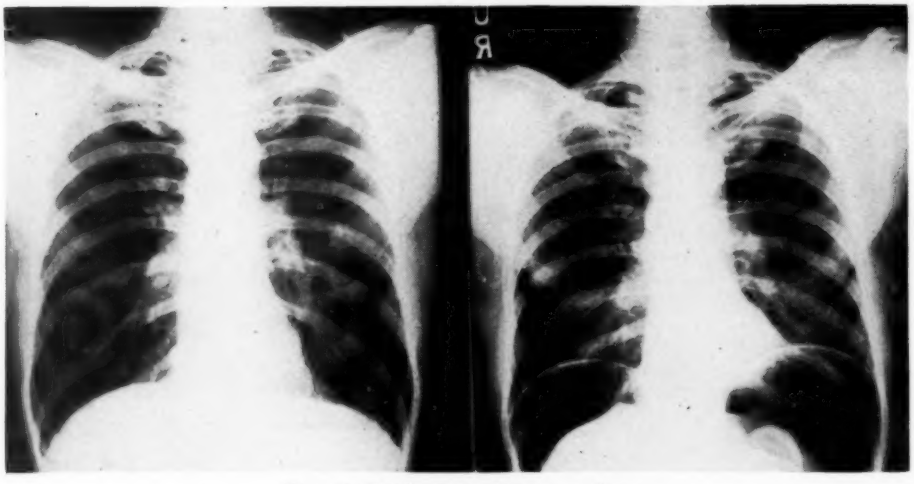

FIG. 8. Patient 7, after one day.

Elevation of the diaphragm in 8 of the patients, one to ten days after the induction of pneumoperitoneum, is shown in Figures 1 through 8. The change was marked in all except Patient 4, in whom moderate elevation occurred.

DISCUSSION

Pulmonary emphysema occurs as a secondary manifestation of conditions of the lungs, bronchi, pleura, heart or chest, and is usually preceded by a long history of chronic bronchitis or asthma, cough and bronchial spasm. The primary pathologic changes in the disease are destruction of the peribronchial and perialveolar elastic fibers, destruction of the perialveolar capillaries, distention of the thoracic cage, relative increase in the size of the lungs, and structural circulatory changes.

Bronchial obstruction and strenuous cough cause an increase in intrapulmonary pressure (4, 5). This results in constriction or obliteration of some of the blood vessels, overdistention of the alveoli, and degenerative changes in the elastic elements of the lungs. Chronic hyperinflation of the lungs follows, accompanied by a decrease in, or disappearance of, the negativity of the intrapleural pressure, depression of the diaphragm, and limitation of the movement of the muscles of respiration. Since the lungs cannot be emptied to a normal extent, the ratio of residual air to lung capacity is reduced, the vital capacity is decreased, and the maximum breathing capacity is always considerably below the estimated normal. Dyspnea appears, apparently because of the reduced ratio of ventilatory work to ventilatory capacity (6). The impairment of the movement of the diaphragm and the intercostal muscles results in defective alveolar aeration.

Carbon dioxide retention and anoxia, the primary biochemical changes associated with severe pulmonary emphysema, reflect the great reduction in ventilatory exchange effected by defective alveolar ventilation, circulatory changes, and the reduction in the total respiratory surface. The severity of the disease can be judged by the degree of arterial anoxia at rest and after the standard exercise (6). Once the arterial blood oxygen saturation falls below 90 per cent at rest, circulatory abnormalities appear: hypervolemia, polycythemia, increase in blood flow, and pulmonary hypertension. Cor pulmonale begins with the stage of pulmonary hypertension.

Pneumoperitoneum should be instituted before these severe pulmonary and circulatory changes appear. After dilatation of the pulmonary artery and hypertrophy of the right ventricle have developed, the procedure may cause respiratory embarrassment. Beck, Eastlake and Barach (7) believe that "in those instances in which right ventricular insufficiency is present, either overt or latent, the increased venous pressure [after pneumoperitoneum] may develop in part as a result of inability to empty the right ventricle under conditions of increased intrapulmonary pressure."

Failure of the right ventricle is only a complication of the pulmonary insufficiency. With early therapy, there is no doubt that the crippling results of pulmonary emphysema can be largely prevented.

SUMMARY

More effort should be made to diagnose and treat pulmonary emphysema in its early stages, when it may be completely reversible. The use of artificial pneumoperitoneum is a particularly promising procedure in cases uncomplicated by cardiac insufficiency. Improvement of the capacity for diaphragmatic breathing after induction of pneumoperitoneum is a constant finding.

Fourteen patients were treated by the process of pneumoperitoneum in an investigation of its effects. They were from 46 to 63 years of age. All of them had far-advanced pulmonary emphysema but no definite evidence of heart failure. After induction of pneumoperitoneum, all except one of the patients experienced considerable subjective improvement. The average range of dia-

TABLE 1. *Summary of Clinical Data on Patients with Pulmonary Emphysema Treated by Pneumoperitoneum*

Patient			Symptoms			Blood Pressure	Venous Pressure	EKG	Bronchoscopic Findings	Improvement	
No.	Age and Sex		Dyspnea	Cough	Sputum					Subjective	Objective
1	64	M	++++	++++	+++	130/88	40	Normal	Partial obstruction	++++	++++
2	50	M	++++	++++	++++	120/80	30	Normal	Partial obstruction	++++	++++
3	58	M	++++	++++	++	142/94	40	Normal	Normal	++++	++++
4	63	M	++++	++++	++	138/90	50	Myocardial damage	Inflammatory changes	++	++
5*	50	F	++++	+	+	152/106	60	Right axis deviation	Partial obstruction	+++	++
6	58	M	+++	+++	++	140/92	30	Normal	Inflammatory changes	++++	++++
7	54	M	++++	++	++	128/82	40	Normal	Normal	++++	++++
8	46	M	++++	+++	+++	124/86	30	Normal	Normal	++++	++++
9	62	M	++++	++++	++	150/94	60	Right axis deviation	Pale mucosa	None	None
10	52	M	++++	+++	++	124/82	30	Normal	Normal	++++	++++
11	56	M	+++	++	+++	128/90	30	Normal	Partial obstruction	++++	++++
12	49	M	++++	+++	++	120/87	40	Normal	Partial obstruction	++++	++++
13	51	M	++++	++++	+++	134/90	50	Normal	Inflammatory changes	++++	++++
14	60	M	++++	+++	+++	150/96	60	Normal	Inflammatory changes	++++	++++

* Cardiac history was negative in all patients except No. 5, who had been treated with digitalis.

phragmatic motion, which was 10 per cent of normal prior to treatment, increased to 40 per cent.

Pneumoperitoneum has a definite place in the management of older patients with pulmonary emphysema. The clinical benefits obtained indicate that this procedure should be considered whenever no positive contraindications exist.

REFERENCES

1. Reich, L.: Der Einfluss des Pneumoperitoneums auf das Lungenemphysema, *Wien. Arch. f. inn. Med.* **8:** 245, 1924.
2. Duomarco, J.; Rimini, R., and Recarte, P.: La presión intraabdominal en al enfisema pulmonar y en la insuficiencia cardíaca congestiva con referencia al problema de la hipertensión torácica, *Arch. urug. de med., circ. y especialid* **25:** 244, 1944.
3. Carter, M. G.; Gaensler, E. A., and Kyllonen, A.: Pneumoperitoneum in the treatment of pulmonary emphysema, *New England J. Med.* **243:** 549, 1950.
4. Banyai, A. L.: So-called hypertrophic emphysema, *Dis. of Chest* **25:** 25, 1954.
5. Banyai, A. L.: The rationale of pneumoperitoneum treatment of emphysema, *Dis. of Chest.* **23:** 695, 1953.
6. Baldwin, E. de F.; Cournand, A., and Richards, D. W., Jr.: Pulmonary insufficiency; study of 122 cases of chronic pulmonary emphysema, *Medicine* **28:** 201, 1949.
7. Beck, G. J.; Eastlake, A. C., Jr., and Barach, A. L.: Venous pressure as a guide to pneumoperitoneum therapy in pulmonary emphysema, *Dis. of Chest* **22:** 130, 1952.

THE EVALUATION OF MAJOR SURGERY FOR CANCER IN THE AGED

THOMAS J. ANGLEM, M.D.* AND MARTIN L. BRADFORD, M.D.

Brookline, Massachusetts

Although there has been some improvement in attitude in the last few years, there is still a strong feeling of reluctance towards surgery in the aged, and this feeling is held not only by patients and their relatives, but also by many physicians. When the surgical problem is cancer, the reluctance is particularly evident.

This attitude stems from three main factors:

1. A past operative mortality rate for the elderly patient that could well be considered prohibitive.

2. Unawareness of the changed prognosis resulting from surgical advances.

3. Unfamiliarity with the actual life expectancy of persons in this age group. Many are surprised to learn that a man of 70 can look forward to living 9.6 years and a woman of 70, to 10.8 years; at the age of 75 the life expectancy for a man is 7.3 years and for a woman, 8.08 years; at 80 the respective figures are 5.4 and 5.83 years; and even at 85, the life expectancy is 4.11 years.

There is an abundance of data that attests to the fact that the population of the United States is simultaneously expanding rapidly and aging. The relation of these two factors to the problem of cancer in the aged becomes apparent at once on considering the numbers of persons in this country past the age of 70 in the years 1900 and 1950, and the projected figures for 1960. This is a matter of major importance because of the tremendous number of persons among whom the incidence of cancer is disproportionately high (Table 1).

The possible effect of the biology of senescence on the behavior of tumors may have a bearing on this problem also. There is a widespread opinion, emphasized many years ago by Finsterer, that, excluding other factors, the prognosis in the elderly cancer patient is likely to be better than average, because cancers developing in this age group are likely to be of a lower grade of malignancy. This thesis appears to be based on general impressions with little documentary support. However, it is supported by the recent experimental work of Lemon (1), who found that tumors transplanted into the cheek pouches of hamsters grew more slowly in the older animals.

We believe that if all the modern surgical safeguards are used, the operative mortality in elderly patients requiring the most major surgical procedures for cancer should be about the same as that in younger patients, and that the prognosis as indicated by the standard five-year survival rate should also compare favorably with that of ordinary-risk patients.

PRESENT STUDY

We are reporting on the follow-up results in 258 patients over the age of 70 who underwent major surgical procedures for carcinoma. All minor operations

* Address: 1180 Beacon Street, Brookline 46, Mass.

TABLE 1

*Population of the United States By Age in 1900, 1950 and 1960 (in Thousands)**

Age (yrs.)	Year		
	1900	1950	1960
70–74	886	3412	4353
75–79	521	2178	3075
80–84	253	1100	1647
85 and more	122	576	762
Totals	*1782*	*7266*	*9837*

* Adapted from Monroe (2).

TABLE 2

General Classification of Cases, Showing Variation in Mortality Rates

	No.	Operative Mortality (%)
Total patients	258	15.1
Total operations	318	12.9
Definitive	277	14.8
Curative	174	11.3
Palliative	84	21.4
Exploratory	19	15.8

TABLE 3

Results of Definitive Operations

	Number
Operative deaths	41
Five-year survival without recurrence	39
Alive without recurrence, 1–5 yrs.	28
Dead without recurrence less than 5 yrs.	16
Dead with cancer	148
Alive with cancer	5
Total	*277*

were eliminated. Two patients were 90 years of age; and 1 of these, who had an anterior resection for carcinoma of the sigmoid, lived fifty-one months without recurrence, finally dying of cardiac failure. Forty-five of the 258 patients were over the age of 80.

Table 2 lists the curative, palliative and exploratory operations, with their corresponding mortality rates. The over-all operative mortality rate was 15 per cent.

Actually, 318 operations were performed, with a mortality rate of 12.9 per cent, but many of these procedures were incidental, *e.g.*, drainage of abscesses, resuture of wounds and surgical treatment of other complications. In order to reach a true mortality rate for the definitive operations, these incidental procedures (and

others such as colostomy closures) were eliminated. The results of the 277 definitive operations are shown in Table 3.

Following the 174 curative operations, 39 patients were living five or more years without recurrence. An additional 28 were alive without disease for less than five years, and 16 died without recurrence within the five-year period (Table 4).

Tables 5 and 6 show the survival years of patients without recurrence, and Table 7 shows the survival rate of patients dead with cancer. Three patients having palliative operations lived from three to five years; and 27 of 70 patients having operations aimed at cure, lived from two to five years before eventually dying of cancer.

TABLE 4

Results of Curative Operations

		Number
Operative deaths		20
Five-year survival without recurrence	39	
Alive without recurrence less than 5 yrs.	28	
Dead without recurrence less than 5 yrs.	16	
Total without recurrence		83
Dead with recurrence	70	
Alive with recurrence	1	
Total with recurrence		71
Total ops.		*174*

TABLE 5

Survival Without Recurrence—Five Years or More

Years Survival	No. of Patients
Five	39
Six	23
Seven	20
Eight	15
Nine	11
Ten	7
Fourteen	2
Total (5 or more yrs.)	*39*

TABLE 6

Survival Without Recurrence—Less Than Five Years Only

Years Survival	No. of Patients
Up to one-half	44
One-half to one	41
One	38
Two	24
Three	14
Four	8
Total (less than 5 yrs.)	*44*

TABLE 7

Survival in Months of Patients Dead With Cancer

Type of Surgery	No. of Operations	Months Survival and No. of Patients Surviving						
		1–6	7–11	12–23	24–35	36–47	48–59	60+
Exploratory	16	13	2	1	—	—	—	—
Palliative	62	34	11	10	4	1	1	1
Curative	70	11	18	14	14	8	4	1
Totals	*148*	*58*	*31*	*25*	*18*	*9*	*5*	*2*

TABLE 8

Percentage of Five-Year Cures in 115 Curative Operations

Site of Curative Operation	No. of Patients Followed 5 Yrs.	No. of Patients Surviving 5 or More Yrs. (no recurrence)	Five-year cure (%)
Head and neck	18 (20 ops.)	9	50.0
Breast	19 (20 ops.)	7	36.8
Gastric	13	4	30.8
Pelvic	9	2	22.2
Cecum and ascend. colon	10	6	60.0
Hepatic flexure, transverse colon and splenic flexure	8	1	12.5
Descending colon	5	0	0
Sigmoid	13	4	30.8
Rectosigmoid	2	0	0
Rectum	12	4	33.3
Axillary and groin dissections	3	2	66.6
Totals	*112 (115 ops.)*	*39*	*34.8*

TABLE 9

Operative Mortality Rates in Five-Year Periods

Period	Avg. Age of Patient (yrs.)	No. of Admissions	No. of Operative Deaths	Operative Mortality (%)
1936–1940	75.2	35	9	25.7
1941–1945	74.0	87	9	10.3
1946–1950	75.7	109	17	15.6
1951–1952	75.9	45*	6	13.3
Totals	*75.2*	*276*	*41*	*14.9*

* One admission. Patient operated on twice for two different cancers.

Table 8 shows the percentage of five-year cures in 115 curative operations, listed according to anatomic regions. The five-year survival rate for 112 patients was 24.8 per cent; and for 141 patients, the three-year survival rate was 39.7 per cent. Although the numbers in each group are small, it is interesting

TABLE 10

Operative Mortality in Curative Operations by Periods

Period	No. of Curative Operations	No. of Operative Deaths	Operative Mortality (%)
1936–1941	14	3	21.4
1941–1946	53	6	11.3
1946–1951	77	9	11.5
1951 & 1952	30	2	6.7
Totals	*174*	*20*	*11.5*

that the five-year survival rates of the patients over 70 for head-and-neck, gastric, right colon, sigmoid and rectal cancer operations compare not unfavorably with the end-results for operations at all ages.

The average age of the patients and operative mortality rates are listed for five-year periods in Table 9. The average age increased less than expected, but showed an increase of 1.9 years from the first period to the last period, whereas the operative mortality rate dropped from 25.7 in the first period to 13.3 in the last period.

Table 10 lists the mortality rates of curative operations by five-year periods and shows a drop from 21.4 per cent in the first period to 6.7 per cent in the last period. The fall in operative mortality was much greater in cases operated on for cure than in those operated on for palliation and exploration. A further decline in operative mortality will depend to some degree upon eliminating useless exploratory and palliative procedures by a most careful and thorough preoperative work-up.

SUMMARY AND CONCLUSIONS

A report is presented of the survival rates in 258 patients 70 years of age or more, who had undergone major surgical operations for cancer. In 168 of these patients (or 65.1 per cent) with an average age of 75 years, undergoing 174 operations aimed at cure of the disease, the operative mortality rate was 11.5 per cent. Of these operations, 115 were performed on 112 patients more than five years previously; thus the 5-year-or-longer survival rate was 34.8 per cent. The three-year survival rate in 141 cases was 39.7 per cent. In the last two years of the study, despite the fact that surgery was more extensive and the patients were somewhat older, the operative mortality rate was reduced to 6.7 per cent.

In view of these findings, and the normal life expectancy of these elderly patients, the benefits of surgery for cancer should not be withheld on the basis of age alone.

REFERENCES

1. LEMON, H. M.: Personal communication.
2. MONROE, R. T.: Effect of aging of population on general health problems, *New England J. Med.* **249:** 277–285, 1953.

TREATMENT OF CANCER WITH TRIETHYLENE THIOPHOSPHORAMIDE AND OXAPENTAMETHYLENE*

JEANNE C. BATEMAN, M.D. AND NANCY J. LARSEN, B.S.

George Washington University, Washington, D. C.

The treatment of cancer is essentially the same for young and old. Primarily it consists of an attempt to eradicate the disease by surgical removal or irradiative destruction of the tumor. Unfortunately only half of the cancer cases discovered today are being diagnosed while localized at the site of origin (1), and beneficial effects of surgery and x-ray therapy are limited in the presence of disseminated disease. Hormones are useful in the treatment of certain types of far advanced neoplasms and their administration has resulted in objective and subjective remissions in approximately 20 per cent and 50 per cent, respectively, of treated patients. Age is not a contraindication for hormone therapy, although the side effects of fluid retention may become a hazard in the presence of diminished cardiac or pulmonary reserve.

The need is great for effective chemotherapeutic agents in the treatment of patients who do not respond or who have become resistant to hormones. Many compounds have been tried both locally and systemically (2). When the hazard of clinical toxicity is great, the short period of remission which is achieved hardly justifies such therapy. In 1953 Shay and his co-workers (3) observed regression of skin nodules in 2 patients with metastatic mammary carcinoma following administration of N-N′-N″-triethylene thiophosphoramide. Although hematopoietic depression must be watched for, this agent has a low order of clinical toxicity.

CLINICAL MATERIAL AND METHODS

The present report concerns 195 patients with a variety of cancers considered far advanced and unsuitable for other forms of therapy, who were treated with N-N′-N″-triethylene thiophosphoramide and N-(3-oxapentamethylene) N′-N″-diethylene phosphoramide. These agents were given intravenously, intramuscularly, intra-arterially, intrapleurally, intraperitoneally, intrapericardially, intracranially, and directly into tumor sites (Table 1).

Of the 195 patients, 122 received triethylene thiophosphoramide, 26 received oxapentamethylene and, because of a temporary shortage, 47 patients were changed from one agent to the other. Triethylene thiophosphoramide[1] was administered in doses of 5 to 40 mg. dissolved in sterile distilled water in a concentration of 10 mg. per cc. Oxapentamethylene[1] in doses of 10 to 80 mg. was similarly prepared in a concentration of 20 mg. per cc. Total doses of drug varied from 15–535 mg. of triethylene thiophosphoramide (average 174 mg.) given in

* Aided by a grant from the Lederle Laboratories Division of the American Cyanamid Company.

[1] Kindly supplied by Dr. James M. Ruegsegger, Clinical Research Section, Lederle Laboratories Division of American Cyanamid Company.

TABLE 1

Chemotherapy of Carcinoma in 195 Cases

Therapeutic Agent	*No. of Cases*
Triethylene thiophosphoramide	122
Oxapentamethylene	26
Both (successively)	47

Route of administration	*No. of Cases*
Intravenous	25
Intramuscular	7
Intra-arterial	2
Intrapleural	30
Intraperitoneal	9
Intrapericardial	2
Intracranial	2
Intra-tumor	133

	Dosage	*Total*	*Average*
Triethylene thiophosphoramide	5–40 mg. every 1–3 wks.	15–535 mg. in 1–485 days	174 mg. in 89 days
Oxapentamethylene	10–80 mg. every 1–3 wks.	20–555 mg. in 1–287 days	147 mg. in 36 days

a period of 1–485 day, (average 89 days), and 20–555 mg. of oxapentamethylene (average 147 mg.) given in a period of 1–287 days (average 36 days). Treatment was administered once every one to three weeks, except early in the course of therapy when semi-weekly injections were sometimes employed. The 2 patients treated intra-arterially received an injection daily; this route is no longer used because other routes are simpler and the results are equally effective. Therapy was administered in the clinic or office, except when given by the intra-arterial route, or if the patient was bedridden. A blood count was made prior to each dose of drug.

RESULTS

Age of the patient

The 195 cases are divided according to primary site of the cancer and age of the patient in Table 2. There were no cases in the first and tenth decades and only 2 each in the second and ninth decades; the largest number occurred in the fifth, sixth and seventh decades. It is of interest that most of the patients with hopelessly advanced cases of mammary cancer in this limited series were between the ages of 40 and 49. This is in contrast with the known increase in the incidence of this disease with advancing years.[2] Our figures suggest that mammary cancer may be more serious in this important age group (40–49 years) than in older women. Although ovarian carcinoma has been described as being a more rapidly fatal disease in young females, in our series the greatest incidence of so-called hopeless cases occurred in the seventh decade. According to Willis (4), pulmonary carcinoma on the average has a special tendency to affect younger people. In the group of patients described here there were 7 far advanced cases of lung can-

[2] National Cancer Institute Survey, 1947–1948.

cer, each in the sixth and seventh decades. These differences from generally accepted concepts may result from the limited number of cases studied. In the entire group, 77 patients were under 50 years of age, and 118 were over 50 years.

Survival rates

Table 3 summarizes the response to therapy and the survival rate in 151 patients with far advanced cancer. The patients are grouped according to primary site of disease, number and percentage improved, number demonstrating objective and subjective improvement, duration of improvement, duration of

TABLE 2. *Distribution by Age and Primary Site of Tumor in 195 Patients Treated with Triethylene Thiophosphoramide and/or Oxapentamethylene*

Age (yrs.)	Breast	Ovary	Uterus	Gen-Ur.	Gast.-Intest.	Lung	CNS	Head & Neck	Melanoma	Misc.	Total
10–19							1				1
20–29	1	1			2		1				5
30–39	8	5	1		2	2		4		2	24
40–49	22	3	3	1	7	5	1	1	1	3	47
50–59	20	3	1	1	5	7	1	5	2		45
60–69	16	9	2	3	6	7	3	3	1	2	52
70–79	6	3		1	4	1		4		1	20
80–89	1										1
Totals	*74*	*24*	*7*	*6*	*26*	*22*	*7*	*17*	*4*	*8*	*195*

TABLE 3

*Results of Phosphoramide Therapy in 151 Patients with Far Advanced Cancer**

Primary Site	No. of Patients	Improved						Survival (months)		No. of Patients Alive
		No.	%	Obj.	Subj.	Duration (months)	Avg. Duration (months)	Range	Avg.	
Breast	65	57	87	52	52	1–14	4.2	1–14	5.0	33
Ovary	19	15	79	14	15	1–14	5.2	1–14	6.0	7
Uterus	5	3	60	3	3	1–5	2.0	1–5	2.2	2
G.U. tract	4	3	75	3	3	1–1.5	1.0	1–3	2.2	2
G.I. tract	18	5	36	4	5	0.5–5	1.7	1–5	3.0	5
Lung	16	10	62	6	8	0.5–1	0.8	1–6	2.8	2
CNS	5	5	100	5	5	2–13	6.9	5–13	8.7	2
Head & Neck	13	8	61	8	4	1–8	2.5	1.5–8	3.5	2
Melanoma	3	1	33	1	0	9	—	3–9	5.3	1
Misc.**	3	0	0	0	0	0	0	2–8	5.0	0

* No patients with survival of less than one month included.

** Included 1 sweat gland tumor, 1 osteogenic sarcoma, 1 metastatic adenocarcinoma of abdomen.

survival, and number alive at the time of writing. Experience has demonstrated the delay in response to the phosphoramide drugs. Since survival of less than one month precludes proper evaluation of these drugs, patients living less than four weeks following institution of therapy have been omitted from this table.

Mammary carcinoma

Patients with mammary carcinoma formed the largest group. All patients were considered inoperable and all had been rejected for irradiation at the time chemotherapy was instituted. Only 8 persons in this group had had no prior treatment. Seventy-two per cent of the patients had been operated on, 72 per cent had received one or more courses of irradiation, and 41 per cent had received one or more types of hormonal therapy including adrenalectomy. Eight patients had been castrated by irradiation, and 7 by surgery. There were 5 cases of bilateral mammary carcinoma treated surgically; in 9 more cases there was late spread of cancer to the opposite breast. Eighty-seven per cent of the patients were improved by chemotherapy, as manifested by regression of soft tissue lesions, pulmonary lesions, healing of ulceration, recalcification of osseous metastases, control of effusions, disappearance of neurologic signs and symptoms and reduction or disappearance of pain, pruritis, dyspnea and cough. Over half of these patients resumed or increased normal activities after institution of therapy. In 11 cases the disease was controlled to the extent that the patients could be actively employed, as exemplified by the following case history:

E.B., a 59-year-old government employee, was first seen in May 1954, at which time she was complaining of severe weakness, cough and dyspnea. She had had a right radical mastectomy in May 1952 (scirrhous carcinoma, duct-cell type), irradiation for skin recurrences in August 1952, and irradiation for infra- and supraclavicular masses in November 1953. Physical examination revealed nodules in the right anterior axillary fold and the posterior neck, and rales at the right lung base. There was x-ray evidence of pulmonary infiltration, and osseous lesions in a rib. The local lesions were injected with triethylene thiophosphoramide. In August 1954 a chest tap was productive of 950 cc. of fluid containing cancer cells. Triethylene thiophosphoramide (20 mg.) was instilled into the pleural space. No cancer cells were present in pleural fluid removed two months later. From May 28, 1954 to January 24, 1955, the patient received 10 mg. of triethylene thiophosphoramide intravenously, 55 mg. intrapleurally, and 220 mg. into peripheral nodules and nodes. Full-time work was continued with a minimum of sick leave during this period. The patient was lost to follow-up eight months later when she retired and moved to another state.

Ovarian carcinoma

Twenty-one patients with ovarian carcinoma were studied; 2 survived less than one month. In 7 patients (33 per cent) both ovaries were involved. Ten patients had been pretreated by surgery alone, and 10 by surgery followed by irradiation. In 1 case diagnosis had been made from a neck-node biopsy and verified at post mortem. The phosphoramide was administered directly into irresectable tumor at operation in 2 cases; at other times it was administered intrapleurally, intraperitoneally, intrapericardially or directly into tumor masses through the abdominal wall or transvaginally. Objective improvement consisted of control of effusions and a decrease in soft tissue masses. The following case

history outlines the course of the disease in a patient who was able to return to work following institution of phosphoramide therapy.

E.J.B., a 39-year-old female, had complained of intermittent abdominal swelling of several months' duration. At laparotomy on June 11, 1954 the omentum, which was shrivelled into a small hard pancake mass by tumor infiltration, was resected. Bilateral proliferative adherent ovarian tumor masses were left in the pelvis but each was injected with 20 mg. of triethylene thiophosphoramide. The postoperative course was not remarkable, except for transient pyelitis due to left ureteral obstruction by the tumor. Subsequently the patient was treated by the intravenous, and then by the transvaginal routes at one-week to three-week intervals, with a total dose of 250 mg. of triethylene thiophosphoramide and 60 mg. of oxapentamethylene. Nine months after operation there was no palpable disease and the patient was working as a secretary.

Miscellaneous groups

Response to phosphoramide therapy by patients with epidermoid carcinoma of the cervix and squamous-cell carcinoma of the urinary tract was limited. However in 1 case of adenocarcinoma of the corpus uteri there was regression of a recurrent mass, and in 1 case of adenocarcinoma of the cervix there was a marked histopathologic change following preoperative treatment.

Twenty-six patients with carcinoma of the gastro-intestinal tract were treated; 8 died or were lost to follow-up in less than one month. Softening of hard tumor masses occurred in 4 patients, and unexpected decrease in pain in 6.

There were 22 patients with carcinoma primary in the lungs or bronchi. In 19 instances the types of carcinoma were as follows: 6 squamous-cell, 2 oat-cell, 4 undifferentiated, 6 adenocarcinoma and 1 anaplastic. In 1 case the pathologic type was undetermined. Two cases were diagnosed from the x-ray findings and the presence of neoplastic cells in the pleural effusion. In the 16 patients who were treated for more than one month, improvement was observed in 62 per cent—with an average duration, however, of only 0.8 month. Duration of survival ranged from one to six months. Two patients are still living.

Four cases of tumor primary in the central nervous system and 1 of metastatic lesion of the cervical cord secondary to an unknown primary were included in this series. All 5 patients showed subjective and objective signs of improvement for periods varying from two to thirteen months. Two are still alive at thirteen months. One 23-year-old female managed her household and cared for her two babies since institution of chemotherapy over thirteen months before. Surgery had revealed a fusiform swelling of the cervical spinal cord. Symptoms had been controlled for five months by local irradiation but had recurred prior to chemotherapy.

A variety of tumors involving the head and neck were treated. The results were discouraging, with a few exceptions. A 33-year-old male with rapidly recurring transitional-cell carcinoma, primary in the frontal sinus, and not controlled by irradiation, received local injections of triethylene thiophosphoramide. The lesions melted quickly but recurred almost as soon. A 68-year-old female had a recurrence of a basal-cell carcinoma at the margin of a huge postoperative facial defect; the recurrent tumor disappeared following local injections of triethylene

thiophosphoramide. A 59-year-old female, admitted to the hospital in extremis from multiple pulmonary metastases secondary to adenocarcinoma of the submaxillary gland, lived for four months while receiving intravenous injections of triethylene thiophosphoramide.

Two cases of melanoma treated with triethylene thiophosphoramide and 1 treated with oxapentamethylene (survival less than one month) showed no objective evidence of improvement. However in a 40-year-old white female with recurrent lesions on a lower extremity following local block and groin dissection, no new lesions developed and several small nodules disappeared in the nine months of therapy with local injections of oxapentamethylene.

A small group of miscellaneous cases was not helped by the phosphoramide drugs.

Toxicity

As reported before (5), clinical toxicity following injection of triethylene thiophosphoramide or oxapentamethylene is unusual. Occasionally pain followed injection into very firm tumor masses. Local administration of small amounts of hyaluronidase added to novocaine and given prior to the phosphoramide injection made the procedure less painful. An occasional unexplained short post-treatment febrile episode was noticed.

Inhibitory effects of triethylene thiophosphoramide on hematopoiesis were limited to leukopenia and occasionally thrombopenia. During oxapentamethylene therapy, inhibition of hematopoiesis was unpredictable and occasionally severe. Although less frequent than leukopenia, there was occasionally a depression of the red blood cells, which appeared as suddenly as that occasionally seen during triethylene melamine therapy; it was associated with leukopenia and thrombopenia.

COMMENTS

Previous observations indicate that triethylene thiophosphoramide is a useful agent in the control of certain far advanced cancers. Response to therapy is slow and maintenance treatment must be continued indefinitely. However, administration can be carried out on an outpatient basis at intervals of one to three weeks. Dosage is limited because of the possibility of hematopoietic depression. Several factors, including prior irradiation or hormonal therapy, influence the hematopoietic reserve. Azotemia appears to cause a marked lowering of the tolerance to the phosphoramides. Age per se does not appear to effect the tolerance. It is possible that the phosphoramides, like other polyfunctioning alkylating agents, increase sodium excretion. Such a physiologic action would be useful in the presence of complicating cardiac disease or hypertension.

Oxapentamethylene was first used with the hope that it would affect a somewhat different spectrum of tumors than does triethylene thiophosphoramide. So far, no such selection has been established, although there may be differences in modality of action between these two phosphoramides. Hematopoietic depression appears to be more unpredictable with oxapentamethylene than with tri-

ethylene thiophosphoramide; red blood cell and platelet counts occasionally drop sharply and somewhat unexpectedly.

Much more study and prolonged observations are needed to define the limits of usefulness of these two phosphoramides. They hold promise of becoming useful tools in the oncologists' struggle against a disease which often is a devastating socio-economic problem.

REFERENCES

1. Cutler, S. J., and Haenszel, W. M.: The magnitude of the cancer problem, *Pub. Health Rep.* (Washington) **69:** 333–338 (Apr.) 1954.
2. Bateman, J. C.: Cancer chemotherapy, *Med. Ann. Distr. Columbia* **24:** 55–62 (Feb.) 1955.
3. Shay, H.; Zarafonetis, C.; Smith, N.; Woldow, I., and Sun, D. C. H.: Treatment of leukemia with triethylene thiophosphoramide, *A. M. A. Arch. Int. Med.* **92:** 628–645 (Nov.) 1953.
4. Willis, R. A.: Pathology of Tumors. London, Butterworth & Co., Ltd., 1948, p. 360.
5. Bateman, J. C.: Chemotherapy of solid tumors with triethylene thiophosphoramide, *New England J. Med.* **252:** 879–887 (May 26) 1955.

THE PROS AND CONS OF ESTROGEN ADMINISTRATION AFTER THE MENOPAUSE*

E. KOST SHELTON, M.D.**

The Shelton Clinic†, Los Angeles, California

One of the controversial issues in clinical medicine concerns the use and/or abuse of estrogenic material during, but especially following, the female climacteric. There is a school of thought which clings to the dictum that the menopause is a time-honored phenomenon to be suffered in silence with fortitude and that any therapy, especially of a hormonal nature, designed to alleviate the symptoms is something of a crime against nature. To support this theory it is argued that: a) most of the symptoms of the menopause and the postmenopausal state are transient, psychogenic, and can be adequately controlled by phenobarbital and/or psychotherapy, b) estrogen prolongs the physiologic adjustment to a changing endocrine economy and should be employed as a last resort, and then only for a brief period, c) endometrial hyperplasia frequently occurs, with resultant uterine bleeding, d) endometrial hyperplasia is a possible precursor of uterine cancer (1), and e) because certain so-called estrogen-dependent tumors of the breast are seen in the premenopausal state (2), it is likely that some otherwise quiescent tissue may be stimulated to malignant activity by estrogen administration in the postmenopausal period. Before critical evaluation of this viewpoint is attempted, it is well to review briefly the role of estrogen in the female body.

Since urinary titers of estrogen are very low in the prepuberal female and fall sharply after the climacteric, it is obvious at the outset that the chief purpose of this hormone is to prepare the organism for procreation. Not only are the mechanics of procreation involved, but all the subtle psychologic factors of feminine desirability, incident to mating, are implicated. As elaboration of the hormone increases, the female is gradually brought to a state of sexual maturity. The rounded contours of the body, soft pliant skin, fully developed breasts, and responsive vaginal tract, are all part of the feminine allure (3). Aside from the physical factors, the female develops a subtle power in her relationship to the opposite sex. This feeling of being desirable and at the same time, of having a hand in the direction of her marital destiny, continues in the physiologically intact woman, throughout her sexual existence. To most women, the ability to not only capture but to hold a husband, but to feel secure and wanted long after the child-bearing period, is as much a part of her ego as was her ability to bear

* Presented before the Graduate Symposium on Geriatric Medicine given by the American Geriatrics Society, New York, N. Y., November 12 and 13, 1954.

** Deceased February 22, 1955. Late Clinical Professor of Medicine, University of California at Los Angeles; Director Emeritus, Endocrine Clinic, Los Angeles General Hospital; Member of the Staff, Harbor General Hospital, Los Angeles, California; and on Consulting Staff, St. John's Hospital, Santa Monica, California.

† Address: 921 Westwood Boulevard, Los Angeles 24, California.

children. One may assume that much of this sense of well-being is engendered by a youthful hormone elaboration. After being flooded with estrogen for thirty or more years, what happens to the female at the menopause? Perhaps it is better to ask, what *can* happen at the menopause, since only from picturing the extremes may one understand the variables?

SYMPTOMS

Total, rapid estrogen deprivation

It has been shown, from both a clinical and a laboratory standpoint, that total estrogen deprivation results in far-reaching if, as yet, little understood changes in the body physiology. Women with ovarian agenesis, oophorectomized women, and women totally devoid of estrogen following the climacteric, have high titers of pituitary gonadotropin in the urine. There are also well delineated cellular changes in the pituitary, but the relationship to endocrine function is unknown. As Fisher (4) suggests, "Not only the secretion of gonadotrophic hormone by the anterior hypophysis but also the mediation of many of the extragenital effects of estrogen may be intimately bound to the demonstration of the significance of these well demonstrated cytological changes in the cells comprising the anterior hypophysis." Through some obscure mechanism, osteoblastic activity is disturbed, with resultant osteoporosis (5). Arthropathies occasionally develop. Serum cholesterol values often rise to levels more frequently observed in the male, with a concomitant increase in coronary atherosclerosis (6). Hypertension is not uncommon. Regressive changes and alterations of the accessory sex characters ensue. All of the organs originally developed and maintained by endogenous estrogen are now left without hormonal support. The skin loses much of its resiliency, and fine wrinkles rapidly appear. The breasts lose their firmness, and become hypoplastic. The vaginal tract becomes dry and atrophic (7). The autonomic nervous system is violently disturbed, ushering in a group of vasomotor phenomena, embarrassing and often frightening to the patient. More to the point, most of these changes are reversible to a remarkable degree with estrogen replacement. Osteoblastic activity may be improved (*see* comment in Case Histories). Serum cholesterol levels in both man and animals have been lowered (8, 9). Functional hypertension is occasionally relieved. Many of the ills of the reproductive system may be alleviated, and the tissues returned to a more youthful status. In addition, estrogen will ameloriate the autonomic storms and assure the patient of a more placid emotional state. This then, is the worst that can happen following total and rapid estrogen deprivation.

Various levels of estrogen deprivation

Everyone is aware, however, that aside from the cessation of menstruation, many women go through the menopause with little evidence of these changes. It is felt that these individuals may elaborate submenstrual levels of endogenous estrogen (as shown by good vaginal cornification) for many years after the cessation of menstruation, or what has been considered the climacteric. In such women the symptoms of estrogen deprivation are slow, insidious, and often

unrecognized. Having observed such fortunate individuals, some physicians (and laymen) feel that those who complain are vapid or neurotic, and that nothing can happen at the menopause which right thinking and phenobarbital will not correct. There is no argument against a cheerful outlook at this period. However, from a purely physiologic standpoint, there must be many levels of estrogen deprivation, just as there are many levels of hypothyroidism, diabetes and other endocrine disorders, in addition to which the constitutional pattern and individual end-organ response make for many symptomatic variables. What one woman may experience in physical and mental anguish may not be understood, or even credited by another.

ESTROGEN THERAPY

The argument that the menopause is a natural phenomenon and should not be tampered with is reminiscent of all such arguments against progressive movements throughout the ages. There is practically nothing in science—from anesthesia to atomic energy—which for a time and by certain groups, has not been considered a device of the devil. Even many of those who fight nature every day by pasteurizing the milk, budding and spraying their fruit trees, and vaccinating their stock and children, still look upon the menopause with a remarkable degree of medical intolerance. The fact that women now live a quarter of a century longer than in the year 1900 (Table 1), that they dress differently, act differently, consider themselves in all matters equal to the male, and wish to be successful and happy marital companions long after their child-bearing period, is rarely taken into consideration.

In view of the extremes of physiologic variation during and following the menopause, there is no rule of thumb concerning therapy. If a woman has no symptoms and presents ample evidence of adequate (if submenstrual) levels of endogenous estrogen, she should perhaps not be treated. If she shows evidence of severe estrogen deprivation, neither phenobarbital nor psychotherapy will

TABLE 1

Expectation of Life at Birth in the United States (Years)

Year	Male	Female	Both Sexes
1900	46.6	48.7	47.6
1910	48.6	52.0	50.3
1920	54.4	55.6	54.9
1930	59.7	63.5	61.4
1940	62.1	66.6	64.2
1948	65.5	71.0	68.0
1949	65.9	71.5	68.4
1950	66.6	72.4	69.2

Source: National Office of Vital Statistics, Department of Health, Education, and Welfare.

"Life Insurance Fact Book, 1953," Institute of Life Insurance, New York 22, N. Y., p. 93.

alleviate her symptoms. Estrogen will. In my judgment, it is a mistake to consider the vasomotor instability as the sole indication for estrogen substitution. The flushing and flashing are mere autonomic manifestations of a profound metabolic change.

Estrogen administration probably does prolong or postpone some physiologic adjustment, both in women who continue to elaborate submenstrual levels of endogenous estrogen and in those under treatment with estrogen, but I know of no particular reason why the so-called endocrine changes must be ushered in by violent psychic and somatic manifestations, or why this phenomenon must occur in the forties or early fifties, and not ten or fifteen years later. I can even conceive that small doses of estrogen administered to needy women might more nearly emulate the status of the symptomless individual who is capable of manufacturing her own. Perhaps nature intended the physiologic adjustment to occur slowly over a period of years, in the presence of a gradually waning hormone output.

Relationship to uterine cancer

In the postmenopausal woman it is sometimes difficult to arrive at a submenstrual, but physiologically effective dose of estrogen, without occasionally inducing temporary endometrial hyperplasia and subsequent bleeding. Aside from the degree of deficiency, the end-organ response is also variable. Early efforts at replacement therapy must be guided by a period of trial and error, during which bleeding may occur. I have never endowed this with any great pathologic significance. However, papers continue to appear incriminating estrogen as being, if not actually carcinogenic, then a precursor of uterine (especially corpus) cancer by the indirect route of endometrial hyperplasia (1). Østergaard (10) says that out of 123 patients with cancer of the corpus uteri, 18 (22 per cent) had received some form of estrogen from one and a half to fifteen years immediately preceding, during and following the menopause. Of Gusberg's (11) 100 selected cases, 22 per cent had received some form of estrogenic preparation for from one year to an indefinite period. At first glance, statistics of such magnitude suggest that estrogen must be an etiologic factor in corpus carcinoma. However, it should be pointed out that these figures do not take into account the millions of women who take estrogen, and never have need to consult the cancer surgeon.

Recent estimates from official government sources indicate that approximately 700 kilograms of estrogenic material are being manufactured or imported in the United States annually (12). This is enough to treat 7 million women with 1 milligram, twice weekly. In 1950, from a total population of 150 million in the United States, there were approximately 15 million women between the ages of 45 and 65 years (13)—the age period when corpus cancer is most commonly observed. If only one-fifteenth of the available total, or 1 million women (a most conservative estimate), had taken some form of estrogen therapy, and the hormone had played an etiologic role in 20 per cent of the 10,590 deaths from (Table 2) corpus cancer in that year, 2,100 deaths might hypothetically be attributed

to estrogen. Yet, this is only 0.2 per cent of the possible 1 million women in this age group who had received such treatment. Such a low percentage certainly does not argue strongly for the etiologic role of estrogen in corpus cancer. Also, it can be seen (Tables 2 and 3) that the death rates from uterine and breast cancer were not significantly different in 1940 and 1950 than they were in 1930, when estrogen was first employed.

This fits in well with our own experience. During the past twenty-five years the members of our group have given estrogen in some form or another (usually orally in small doses) to several hundred women in whom it was indicated, for periods ranging from two to eighteen years. A careful history, and physical and pelvic examination preceded treatment in every case. We also urged the patients to come in for a follow-up every six months, but their return visits averaged about once a year. Although our gynecologists see the usual run of pelvic pathologic conditions requiring surgery, we have not seen one patient with cancer of the corpus uteri who was taking, or had been taking estrogen. This is so startling—being less of an incidence than one might expect by chance in such a group—that we cannot help wondering if something in our approach does not possibly discourage, rather than stimulate the development of corpus cancer. It should be emphasized that our usual dosage level is in the realm of 0.625 to 1.25 milligrams of estrone sulfate (or its equivalent) daily, and that bleeding is only infrequently observed when this dosage is interrupted periodically. We do not, therefore, feel that endometrial hyperplasia is being induced, except in the occasional unusually sensitive patient. Neither have we seen a patient in this latter group who has continued to bleed when treatment has been temporarily discontinued and later reinstituted at a lower individualized dosage level. The question of the so-called high incidence of uterine malignancy, coexisting with prolonged estrogen elaboration, femininizing ovarian tumors and uterine fibroids, has been most effectively answered by Emge (14). He points out that in a large number of uteri removed by hysterectomy and at autopsy, the coexistence of

TABLE 2

Death Rates per 100,000—Cancer of Uterus (White)

Age Group	Year: 1930	1940	1950
35–44	26.4	24.7	22.9*
45–54	56.9	49.8	54.3*
55–64	85.1	72.9	83.1*
65–74	104.6	100.5	107.1*

* Statistics for "Uterus" not available. Recorded as "genital organ."

Sources of Data

Vital Statistics—Special Reports

Vol. 32, No. 3, July 19, 1950.

Vol. 36, No. 14, March 21, 1952.

Vol. 37, No. 11, November 2, 1953.

From U.S. Department of Health, Education, and Welfare, USPHS, National Office of Vital Statistics.

TABLE 3

Death Rates per 100,000—Cancer of Breast (White)

Age Group	Year: 1930	1940	1950
35–44	18.0	19.1	20.8
45–54	44.8	47.3	47.1
55–64	75.4	76.0	70.9
65–74	93.1	106.4	96.3

Sources of Data

Vital Statistics—Special Reports

Vol. 32, No. 3, July 19, 1950.

Vol. 36, No. 14, March 21, 1952.

Vol. 37, No. 11, November 2, 1953.

From U.S. Department of Health, Education, and Welfare, USPHS, National Office of Vital Statistics.

cancer with such lesions is no greater than that expected by chance. A few years ago, I examined an 80-year-old spinster at the Los Angeles General Hospital Endocrine Clinic, who began menstruating at the age of 11 and, without benefit of any medication, had never missed a period in sixty-nine years. The gynecologic department, suspecting an ovarian tumor, could not find any pathologic lesion in the patient and neither could we. She had the skin, vaginal mucosa, skeletal framework and spirit of the average woman in her fifties, and presented no complaints.

Relationship to breast cancer

So far as the probability of activating breast cancer by estrogen administration after the menopause is concerned, I am as confused as everyone else appears to be. Although it sometimes appears possible that malignant conditions of the breast may be stimulated by estrogen in the premenopausal state (2), it also appears to be true that, after the menopause, this type of cell is no longer estrogen-dependent, but in many cases actually estrogen-phobic, and does not thrive in the presence of circulating estrogen. Thus, Huseby (15) and other surgeons feel that in inoperable malignant lesions of the breast after the menopause, estrogen administration is the treatment of choice. We occasionally see patients with mammary malignancy following the menopause, who have been taking some form of estrogen for periods of months or years, but in our experience the incidence of such malignancy is no greater in the estrogen-treated group than in those who have never received a dose of estrogen. Recently we had the following experiences:

L.B., aged 63, was given a small daily dose of estrogen by mouth, for violent symptoms of the menopause with psychopathic components in 1943 (age then, 52). In 1952, while living in a distant city, a small lump developed in her right breast. She was given a lecture by a local physician about the dangers of estrogen, and discontinued it. After a two-year period without benefit of biopsy or medical advice, she again consulted us with an inoperable cancer of the right breast. The cancer specialist, to whom we referred her, treated her with irradiation and large doses of estrogens.

Relationship to aging, osteoporosis and hypertension

The following case histories illustrate these points:

N.M., a married white woman now aged 63, had consulted us in 1936 at the age of 46, suffering from cardiac palpitation and severe pitting edema of her legs and ankles. Cardiac and renal functions were found to be normal and there were no other pertinent findings. She was a very beautiful woman with a pink-and-white complexion and honey-blond hair, who had been extremely companionable with her husband in every way for twenty-two years. Aside from a hysterectomy for fibromyomata, at the age of 35, her history was otherwise irrelevant. Following the menopause at age 45 the vagina became rapidly atrophic and intercourse painful. The husband, who was not too stable a character and highly sexed, used the opportunity to look about for more youthful companionship.

Estrogens were employed in various forms at first, but eventually conjugated estrogen was used in a daily oral dosage which she continued ever since. The general symptomatology improved remarkably and even the edema disappeared. She and her husband early became reconciled and reportedly continued to have a happy sex life.

At the age of 63, and thrice a grandmother, she is frequently taken for a woman of 40. Her breasts are as firm as they were in her youth and her skin, hair, and vaginal tract show only slight evidence of deterioration.

If this is estrogen "addiction," more women should try it, especially those who have had hysterectomies, in whom bleeding is no problem.

E.M., a married white woman, aged 64, consulted us first in 1945 at the age of 54, complaining of pain in the knees and back, and great fatigue. She had ceased menstruating at 49 (five years before we saw her). The vasomotor symptoms at the time of the menopause were said not to have been severe, but the patient deteriorated rapidly. The physician at the first examination said, "This is an aged looking, kyphotic individual, who appears to be at least 65 years old, 10 years more than her stated age." She was moderately hypertensive, with a blood pressure of 160–180/90. The total blood cholesterol level was 250 mg. per 100 ml. Results of other laboratory tests were not relevant. The findings on pelvic examination, aside from marked vaginal atrophy with petechial hemorrhages and a smear devoid of cornified epithelial cells, were negative. Roentgenograms revealed mild osteoarthritis of the major joints, and osteoporosis of the spine with marked changes in the intervertebral discs. There were a few other non-relevant findings, such as a diaphragmatic hernia and diverticulosis of the descending colon.

The patient was given ethinyl estradiol to the limit of tolerance. She bled a few times and then there were no further untoward symptoms. We have observed her every six or twelve months since the initial examination. She continues to take estrogen. At a recent examination she looked younger than she did ten years ago. The patient had no further back pain after three years of treatment but considerably more osteoarthritis has developed. She stated that she and her husband (a much younger looking, virile man) had resumed normal sexual relations after a period of unhappiness as a result of the patient's disinterest ten years before. She has about the same degree of hypertension as at the first examination.

It is claimed that the administration of estrogens for osteoporosis in the human is purely empirical. However, if the withdrawal of estrogen from the human economy can result in osteoporosis by osteoblastic suppression, it is reasonable to assume that the process is in some degree, reversible. By comparing the life expectancy of the mouse, in which such a process of healing has been well demonstrated, one would have to expect a number of years to elapse in the human before such a prolonged process would become apparent. It is possible that

clinical researchers expect roentgen evidence of mineral re-deposition after estrogen substitution, too soon, since the process is very slow in the human. A large percentage of the bone must be involved before osteoporosis becomes apparent, or before healing can be effectively demonstrated in a roentgenogram. At any rate, demineralization is but a small part of the known metabolic change at the menopause. If the process is only curtailed, or the pain relieved for a number of years, it is probably important to the woman.

A.C., a married white woman, aged 66, consulted us in 1939, at the age of 52 years (three years past the menopause) suffering from severe headaches, numbness in the left arm and leg, hot flushes, sweats, depression and hypertension. Aside from the blood pressure, which was labile and varied from 180/90 to 200/120, results of examination were essentially negative. Although the elevated blood pressure was considered functional, at times it became alarming. An excerpt from one of her husband's letters dated February 5, 1940 was as follows: "She felt all right until retiring at 10:00 P.M. She began to have headache, dizziness, diplopia, and difficulty in speaking. Her lips seemed "wooden" and she was shortly unable to speak at all. A few moments after these things started she had a slight nystagmus when asked to look to the right or left. The time in which she was entirely "out of the picture" was probably five to eight minutes. As I explained to you, she was seen by a neurologist who arrived about the time her symptoms began to clear, and he stated that he felt sure it was entirely vascular spasm. This of course, has proved to be true. However, I thought at the time that she was surely falling into an apoplexy." Her husband, a well known physician on the Pacific Coast, had tried unavailingly to relieve her. The family history so far as atherosclerosis was concerned, was bad. Her mother died in her early sixties of a coronary attack, and her father died of cerebral hemorrhage at the age of 43.

The patient was given fairly large doses of estrogens (*e.g.*, Progynon, stilbestrol) in an attempt to suppress pituitary function. At the time it was felt that overactivity of this organ probably accounted for her difficulties. I saw her from time to time, throughout the years, during which she improved and the blood pressure stayed around 150–160/85. Not having heard from her for several years, I wote to her husband in a distant city with fear and trepidation in 1954, asking him for a report of her health. He reported that she was well, free of headaches, and that her blood pressure ranged around 160/80, so long as she took the estrogen.

This improvement may well have occurred without the estrogen, but it would be hard to convince the husband that this might be the case, since she was ill for several years before she was seen by us.

DISCUSSION

I am not so naive as to contend that estrogen alone brought about all the good results in the patients whose case histories have been reviewed. These were not clinically controlled observations. Numerous other measures, such as vitamins, high protein diets and occasionally, androgens, were prescribed for these women. As a concomitant of good nutrition, a positive nitrogen balance and a cheerful outlook, however, estrogen has no therapeutic peer in the postmenopausal period, since many of the presenting symptoms are irreversible or not preventable by any other means.

Neither statistically, nor in my own experience, is there evidence to warrant the assumption that estrogens judiciously employed during the postmenopausal period, will cause cancer or any other dire disorder. The argument that estrogen

is often improperly employed is no valid argument against its use. By the same token, one would have to dispense with aspirin, digitalis, antibiotics, and a host of other drugs and hormones. Since estrogenic material is being manufactured and used in large quantities, and will probably continue to be employed, it would seem better to learn how to use it judiciously as a gerontologic measure, rather than be entirely nihilistic about the entire subject of the aging female. It is felt that all women cannot casually be thrown into a common pool just because they are in their late forties or early fifties and cease to menstruate. Continued endogenous elaboration of estrogen, as against complete estrogen deprivation, together with the individual end-organ response, make for a variable symptomatology. In some, the somatic changes are rapid and severe; in others, insidious and barely discernible. Although severe vasomotor phenomena frequently usher in the more severe changes, they are by no means the sole index of the degree of metabolic disruption.

Man's increase in life expectancy has been brought about by a constant fight with nature. All of the preventive measures in medicine, from the cradle to the grave, are designed against the so-called immutable law of the survival of the fittest. If, by scientific insight, the female is destined to live a quarter of a century longer now than she did in 1900 (Table 1), anything which will help to postpone the aging process, lend zest and happiness to her remaining years, and at the same time, is not injurious to her health, should be employed. I feel that estrogen will do this for a certain percentage of women. Need I reiterate that all patients should be carefully examined and followed during estrogen administration? The smallest dose orally which will accomplish the desired result without inducing the untoward effect of uterine bleeding, is recommended.

To me it seemed strange to contemplate a recent paper in the *Journal of the American Medical Association* (7), in which a whole paragraph is given over to the physical changes commonly observed in postmenopausal women, and in which the author ultimately concludes that "the only valid criteria for treating the menopause are the vasomotor flushes, sweats, and flashes." For a number of years, I have tried to understand the difference of opinion between the gerontologically-minded internist and the gynecologist, regarding the use of estrogen as a deterrent to the aging process. Recently, in looking over some old copies of *Endocrinology* I came upon the following statement: "In this brief review I have indicated in a superficial way, only a few of the more important points at which endocrinology and gynecology come into more or less intimate contact. The field of endocrinology is the whole living body—that of gynecology, as of other specialized branches of medical or surgical science, is often confined to a special region. And that is just the point upon which I would like to put a final emphasis—that the gynecologist whose range of vision is so limited as not to extend beyond the ileo-pectineal line will not only miss much of the fascination he might otherwise find in his work, but that, encircling himself with such a narrow horizon, misinterpret or perhaps overlook clinical manifestations which are at times veritable signboards as to therapeutics." (16).

That, ironically, is much better than I could state it.

CONCLUSIONS

Severe physical changes over and above those incident to natural aging occur in a certain percentage of postmenopausal women.

Some women devoid of symptoms apparently continue to elaborate submenstrual levels of estrogen or estrogen-like substances for a number of years after the menopause (cessation of bleeding).

Neither from our experience, nor from government statistics, has estrogen been shown to be carcinogenic or a precursor of carcinoma in the postmenopausal period.

Since women now live twenty-five years longer than at the turn of the century, any treatment which will postpone somatic and emotional deterioration and not endanger their health should be employed.

Estrogen, when combined with other gerontologic measures, is such a therapeutic agent.

REFERENCES

1. Novak, E. R.: Relationship of endometrial hyperplasia and adenocarcinoma of the uterine fundus, *J. A. M. A.* **154:** 217 (Jan. 16) 1954.
2. a) Pearson, O. H.; West, C. D.; Min, C. L.; MacLean, J. P., and Treves, N.: Endocrine Therapy of Metastatic Breast Cancer. Brochure published with Scientific Exhibit, Annual Session, American Medical Association, San Francisco, California, June 1954.
   b) Nathanson, I. T.: The relationship of hormones to diseases of the breast, *Surgery* **16:** 108 (July) 1944.
3. Shelton, E. K.: The use of estrogen after the menopause, *J. Am. Geriatrics Soc.* **2:** 627 (Oct.) 1954.
4. Fisher, J. J.: The extragenital effects of estrogen, *Obst. & Gynec. Survey* **9:** 481 (Aug.) 1954.
5. Albright, F., and Reifenstein, E. C., Jr.: The Parathyroid Glands and Metabolic Bone Disease. Baltimore, The Williams & Wilkins Co., 1948, p. 150.
6. Wuest, J. H., Jr.; Dry, T. J., and Edwards, J. E.: The degree of coronary atherosclerosis in bilaterally oophorectomized women, *Circulation* **7:** 801 (June) 1953.
7. Novak, E. R.: The menopause, *J. A. M. A.* **156:** 575 (Oct. 9) 1954.
8. Pick, R.; Stamler, J.; Rodbard, S., and Katz, I. N.: The inhibition of coronary atherosclerosis by estrogens in cholesterol-fed chicks, *Circulation* **6:** 276 (Aug.) 1952.
9. Barr, D. P.; Russ, E. M., and Eder, H. A.: Influence of estrogens on lipo-proteins in atherosclerosis, *Tr. A. Am. Physicians* **65:** 102, 1952.
10. Østergaard, E.: Estrogens in the etiology of cancer of the corpus uteri, *in* Prophylaxis in Gynecology and Obstetrics, Proc. Internat. Congr. on Gynecology & Obstetrics, Geneva, Switzerland, July 26–31, 1954, pp. 222–228.
11. Gusberg, S. B.: Adenomatous hyperplasia as a precursor of corpus cancer, *Ibid.* pp. 215–221.
12. Jewell, J. B.: Personal communication, February 10, 1953.
13. Official 1950 Census of the United States.
14. Emge, L. A.: Geriatric aspects of primary endometrial cancer, *J. Am. Geriatrics Soc.* **2:** 553 (Sept.) 1954.
15. Huseby, R. A.: Estrogen therapy in the management of advanced breast cancer, *Am. Surgeon* **20:** 112 (Feb.) 1954.
16. Novak, Emil: Some points of contact between endocrinology and gynecology, *Endocrinology* **2:** 438 (Oct.–Dec.) 1918.

THE RATIONALE OF TREATING BENIGN PROSTATIC HYPERTROPHY WITH COMBINATIONS OF TESTOSTERONE AND ESTROGEN

S. J. GLASS, M.D.

Cedars of Lebanon Hospital, Los Angeles, California

Since the therapeutic advent of the sex steroid hormones, sporadic clinical reports have appeared in which testosterone or estrogen was administered to men with benign hypertrophy of the prostate. The results in most of these clinical experiments favored the use of testosterone, but not of estrogen. However, negative results after therapy with testosterone and with estrogen were reported by Heckel (1). Moreover, neither Heckel nor Moore and McLellan (2) found any histologic changes in the hormone-treated prostate. Nevertheless the clinical consensus favors the idea that testosterone may induce symptomatic relief in many men with prostatic obstructive symptoms, regardless of whether this benefit is derived from androgenic effects on the prostate directly or from improvement in bladder function.

Since the work of Huggins and his associates (3), the clinical use of testosterone in men over 40 has become suspect because of its alleged carcinogenic potentialities in the prostate. This presumed hazard particularly applies to men with benign hypertrophy of the prostate, because some pathologists report finding occult malignant foci in the prostate of 20–30 per cent of men over 40 years of age. One might seriously question the significance of such malignant foci, as neither Heckel (1) nor Lesser *et al.* (4) reported any cancer developing in the men treated by them with substantial doses of testosterone for prolonged periods of time. Thus Heckel gave up to 3,790 mg. of testosterone propionate during a period of fifty-six weeks and Lesser *et al.* gave testosterone propionate to 100 men intramuscularly in doses of 25–75 mg. per week for periods varying from three months to four years without mishap. Lesser did observe cancer in one 80-year-old male seven years after termination of the androgenic therapy. Moore and McLellan (2) also reported that the injection of 285–1,125 mg. of testosterone propionate in from twelve to ninety-five days resulted in no significant histologic alteration in the hypertrophied prostate. However, they did find that 15,000–140,000 i.u. of estradiol benzoate given for ten to thirty-one days induced conspicuous alteration in the urethral and ductal epithelium but little if any change in the hypertrophied tissues of the prostate.

That latent malignant foci in the prostate have not been stimulated into overt cancer by large doses of testosterone is somewhat reassuring. Therefore, it may be even more assuring to consider the results following administration of small doses of testosterone, especially when buffered with minimal doses of estrogen.

The rationale of such combined testosterone-estrogen therapy is based on the following considerations. Since benign prostatic hypertrophy usually becomes manifest after testicular function begins to regress, it is logical to assume that sex hormone imbalance or deficiency contributes a specific stimulus to the dis-

ease; and since the testis secretes both testosterone and estrogen it is likely that both hormones are necessary for balance and may together act beneficially on the prostate. In therapy, the added estrogen may also tend to check an unduly sensitive prostate which is over-responsive to testosterone. Another major consideration is the need for some simple and inexpensive long-range hormonal therapy which can be provided with safety, not only for the symptomatic relief from obstructive urinary symptoms associated with benign hypertrophy of the prostate, but also for the prevention of some of the systemic degenerative changes of senescence, notably atrophy of the skin, bones and muscles. To this end, a tablet combining small doses of both testosterone and estrogen is ideally suited.

In about fifteen years of experience with combined testosterone-estrogen therapy for the menopausal syndrome (5, 6), and in the current therapeutic trials in cases of benign prostatic hypertrophy, the author has not experienced any significant complication so long as the dosage of both hormones is kept well within the physiologic range. In these situations of long-range therapy it is incumbent upon the clinician always to seek the minimal effective maintenance dose of hormone—one that provides, not total replacement, but rather a supplement to waning gonadal function. Complications will inevitably follow the administration of large unphysiologic doses of *any* hormone.

CLINICAL MATERIAL AND METHODS

These considerations prompted the author to test the effect of small doses of oral combined testosterone-estrogen therapy in 23 men with the urinary obstructive symptoms of benign prostatic hypertrophy.

The diagnosis was first established in the urology clinic. Here acute urinary obstructive symptoms and infection were treated by conventional methods, such as catheterization, prostatic massage and the administration of antibiotics. Treatment with androgens and estrogens was then instituted in the following sequence. First, placebo tablets were provided in order to determine the validity of the patients' responses. Then individual buccal tablets[1] of estradiol or diethylstilbestrol (0.25 mg.) and methyltestosterone (5–10 mg.) were used interchangeably with placebo tablets, each being given for approximately four to six weeks. Progressively larger doses (up to 0.75 mg.) of either diethylstilbestrol or estradiol were provided singly and then in combination with testosterone (10–30 mg.) daily to determine the optimum effective dose of both hormones which would best control obstructive symptoms or bladder atonicity and thus reduce the volume of residual urine. Likewise single tablets[2] combining both hormones were tried for periods of one or two months before examination was routinely repeated. Repeat examination usually determined changes in sex or bladder func-

[1] Alpha-estradiol and methyltestosterone (Oreton M) were supplied by Schering Corporation, Bloomfield, N. J. Diethylstilbestrol and methyltestosterone were supplied by Eli Lilly and Co., Indianapolis, Ind.

[2] Tylosterone (methyltestosterone 5.0 mg. + diethylstilbestrol 0.25 mg.) was kindly supplied by Eli Lilly and Co., Indianapolis, Ind. Test-Estrin (geriatric) (testosterone 7.5 mg. + estradiol 0.25 mg.) was supplied by the Marlyn Co., Los Angeles, Calif.

tion (frequency, ease of voiding, volume of residual urine) and the character of the prostate (size, shape, mobility and consistency).

Estrogen dosage was sharply reduced when some men manifested undue sensitivity of the breast (mastalgia) and several complained of impairment of libido and potency. On the assumption that these men also might be suffering from latent hepatic insufficiency with impaired hepatic inactivation of the exogenous estrogen, a nutritional regimen (7) was also prescribed. Testing of liver function (bromosulphalein, thymol turbidity, glycogen storage and prothrombin values) showed only borderline deviations from normal in these men. Lipoprotein studies were carried out simultaneously and have been reported elsewhere (8, 9).

Combined testosterone-estrogen tablets[2] were taken twice daily until marked symptomatic relief was obtained. Then only one tablet daily was provided, for maintenance therapy. This was carried out in sequences of five weeks, followed by one week without hormones, in order to minimize hormonal cumulative effects.

RESULTS

Therapeutic trials with more than one drug are not easily evaluated. However, it soon became evident in this study that three distinct responses could be observed.

1. The first was that the placebo tablets provided no symptomatic relief. When placebo tablets were given after the hormone medication, continued benefit was sustained for a short interval.

2. The estrogen therapy was followed by mixed responses when first provided in tablets of 0.25–0.75 mg. daily. Many patients reported some amelioration of symptoms, but improvement was not marked or sustained in any of these patients. Moreover, suppression of sex function was complained of by 3 patients and mastalgia by 4 after six weeks of such treatment. Painful mammary nodules of about 2–3 cm. appeared in 2 of the men. Withdrawal of estrogen was followed by regression of the nodules, but the loss of libido persisted in 2 of these subjects, even after replacing the estrogen with testosterone. Several patients complained of aggravation of obstructive symptoms following estrogen therapy for one or two months. One of these men required transurethral resection after only 60 mg. of estradiol and diethylstilbestrol given in three months.

3. In direct contrast to these rather indifferent responses to estrogen therapy, satisfactory symptomatic relief was obtained in most of the patients following the administration of modest doses of buccal testosterone (Table 1). After testosterone was again replaced by estrogen in daily doses of 0.25 mg. to 0.5 mg., there was a definite tendency to recurrence of obstructive urinary symptoms within one month.

Combined hormone therapy. The addition of 10–20 mg. of buccal testosterone to the estrogen restored the beneficial responses, not only with respect to improved bladder function but also with respect to general well being.

By trial and error, the optimum dose of combined estrogen-testosterone could be determined for each patient. The optimum ratio of combined hormones was

TABLE 1

Treatment of Benign Hypertrophy of the Prostate With Combined Testosterone and Estrogen

Patient	Age (yrs.)	Duration of Therapy	Testosterone (mg.)	Estrogen (mg.)	Results
J.F.	64	3 mos.	0	60	T.u.r.*
W.M.	76	3 mos.	750	23	Good
H.O.	63	3 mos.	800	20	Good
I.S.	75	3 mos.	450	20	Good
J.L.	78	4 mos.	600	15	Good
C.P.	67	4 mos.	1,600	60	T.u.r.*
M.B.	70	5 mos.	1,200	45	Good
J.S.	68	6 mos.	700	45	Good
S.B.	66	7 mos.	1,800	83	Good
S.P.	57	7½ mos.	1,800	83	Good
F.M.	61	10 mos.	3,900	170	Good
H.K.	70	11 mos.	3,700	90	Good
S.P.	75	11 mos.	1,200	43	Good
A.L.	77	13 mos.	2,000	115	Good
M.A.	82	13 mos.	2,800	120	Good
M.B.	68	14 mos.	4,600	135	Good**
H.S.	58	16 mos.	4,800	128	Good**†
S.B.	72	18 mos.	4,500	210	T.u.r.*
I.L.	74	22 mos.	4,700	115	Good
I.S.	77	26 mos.	6,500	175	Good
B.G.	69	30 mos.	5,700	285	Good
J.P.	74	31 mos.	4,350	160	Good**
C.A.	78	4 yrs.	8,400	255	Good

* Transurethral resection.

** Transient gynecomastia.

† Transient impotence.

found to be estrogen (estradiol or diethylstilbestrol) 0.25 mg., with testosterone 5–10 mg., given once or twice daily depending upon the severity of symptoms. One daily dose sufficed for long-term maintenance therapy.

Combined hormone medication resulted in a sharp reduction in urinary frequency and residual volume and more efficient voiding in 20 cases, but changes in the character of the prostate were rather elusive to the untrained fingers of the author (not a urologist). At times the hypertrophied and nodular gland seemed to diminish in size. Likewise the consistency of the gland varied from time to time, changing from soft to firm and occasionally vice versa. Secretory changes within the gland make variability in the consistency understandable. However, the positive responses of improved bladder function and improved general well-being were consistent with the administration of this combined hormone therapy.

When placebo tablets replaced the hormones, or when treatment was discontinued for any reason, there was a slow progressive relapse to the original status. However, after 9 patients completed one year of hormone therapy, the

urinary obstructive symptoms were much milder and were well tolerated without further treatment for another six months.

Irregular responses were experienced by 2 patients after adequate trials of hormones. Temporary improvement in bladder function gave way to a progressive increase in residual urine, necessitating transurethral resection for permanent relief.

At no time could the examiner palpate any areas in the prostate which would suggest the presence of a malignant lesion.

DISCUSSION

Conservative combined androgen-estrogen therapy appeared to be clinically useful in providing these men with symptomatic relief from uncomplicated benign prostatic hypertrophy. There was no evidence that such therapy was followed by any significant complication. In fact the hormone treatment outlined in this study seemed to minimize or prevent unfavorable changes in the bladder, in the musculo-cutaneous and skeletal systems, and perhaps also in the prostate itself. Since prostatic hypertrophy follows regressive changes in the testis, the early exogenous provision of the testicular hormones (testosterone and estrogen) in physiologically small supplemental dosage should be beneficial rather than harmful to the prostate.

However, since the actual cause of benign hypertrophy of the prostate remains unknown, one must regard the rationale for hormone therapy in this situation as theoretical. The treatment should be reserved for selected patients, especially those who for one reason or another cannot be treated surgically. Treatment with hormones should be preceded by a careful diagnostic survey, in order to be sure that malignancy does not exist, and should be instituted only after such conditions as genitourinary infection or calculi have been cared for adequately.

The beneficial responses to combined testosterone-estrogen therapy continue as long as the dosage is kept at a conservative level. The daily maintenance dose arrived at by trial and error in this study (testosterone, 5–10 mg., plus estrogen, 0.25 mg.) seems to be optimal for long-range therapy. Combining both hormones in the small dosage employed provides an adequate physiologic supplement—one which neither overstimulates nor suppresses the accessory sex organs.

This pilot study suffered from certain obvious deficiencies. The first was a lack of a sufficient number of patients. The second was the absence of any histologic evidence, obtained from prostatectomy or biopsy, to determine the morphologic changes within the prostate following variable periods of combined hormonal therapy. Another major handicap was the lack of precise methods for measuring the size of the prostate; thus significant changes in the size could be estimated with only rough approximation. All of these deficiencies can, and should be remedied by urologic research teams.

Notwithstanding the obvious limitations, it was gratifying to observe favorable responses in most of the men treated with combined testosterone-estrogen (Table 1). Only 3 out of 23 required transurethral prostatectomy. How many more were spared surgery because of the organotherapy is difficult to estimate

at this time. Such medical management should be tried in a larger number of patients with more precise methods of determining changes in bladder and prostatic functions. However, insofar as present evidence shows sex hormone treatment to be safe for men with benign hypertrophy, combined testosterone-estrogen therapy may become a welcome addition to the urologic armamentarium.

Even though no malignant changes have been induced by combined testosterone-estrogen medication (nor by testosterone, as reported by Heckel and by Moore and Lesser), it is nevertheless incumbent upon the clinician administering sex hormones to be eternally vigilant for such a possibility.

These limited experiences, as well as the theoretical considerations, suggest that combined testosterone-estrogen therapy may be beneficial for the medical management of uncomplicated benign prostatic hypertrophy, especially when surgery is contraindicated.

SUMMARY AND CONCLUSIONS

Twenty-three men with benign hypertrophy of the prostate were subjected to therapeutic trials with oral combined estrogen-testosterone in small dosage, preceded by trials with each hormone singly. Marked symptomatic relief was obtained by 20 of the patients after daily doses of the combined medication in the proportion of 5–10 mg. of testosterone to 0.25 mg. of estrogen for variable periods averaging about twelve months. No significant complications were observed in these 20 men when the ratio of the two hormones was maintained in this range.

In some men mastalgia, gynecomastia and impotence followed the administration of estrogen alone in a dosage of 0.5–0.75 mg. daily for six to eight weeks. One patient manifested increasing obstruction after only 60 mg. of estrogen given in three months and required transurethral resection for relief.

Irregular, and finally poor responses followed the combined hormone therapy in 2 men who required transurethral resection for permanent relief.

The favorable results obtained in this pilot study suggest that conservative therapy with combined testosterone-estrogen can afford satisfactory symptomatic relief to many men suffering from benign hypertrophy of the prostate, especially when surgery is contraindicated.

Acknowledgment

The cooperation and assistance of the staff in the urology clinic on the service of Dr. J. S. Rubin and of Dr. Lester Riskind are gratefully acknowledged.

REFERENCES

1. Heckel, N. J.: Evaluation of sex hormones in the treatment of benign prostatic hypertrophy, carcinoma of the prostate and other diseases of the genito-urinary system, *J. Clin. Endocrinol.* **4:** 166–172, 1944.
2. Moore, R. A., and McLellan, A. M.: Histologic study of the effect of sex hormones on the human prostate, *J. Urol.* **40:** 641–657, 1938.

3. Huggins, C., and Hodges, C. V.: Studies on prostatic cancer, *Cancer Res.* **1:** 293–297, 1941.
4. Lesser, M. A.; Vose, S. N., and Dixey, G. M.: Effect of testosterone propionate on the prostate gland of patients over 45, *J. Clin. Endocrinol. & Metab.* **15:** 297–300, 1955.
5. Glass, S. J., and Shapiro, M.: Androgen and estrogen in the menopause, *GP* **3:** 39–42, 1951.
6. Glass, S. J.: The advantages of combined estrogen-androgen therapy of the menopause, *J. Clin. Endocrinol.* **10:** 1616–1617, 1950.
7. Glass, S. J., and Lazarus, M.: Improved fertility and prevention of abortion after nutritional-hormonal therapy, *J.A.M.A.* **154:** 908–910, 1954.
8. Glass, S. J.; Engelberg, H.; Marcus, R., and Gofman, J. W.: Effect of estrogens on serum lipids and low density lipoproteins in men and women, *Proc. Soc. Exper. Biol. & Med.* **80:** 264–265, 1952.
9. Engelberg, H., and Glass, S. J.: The influence of physiologic doses of the sex steroid hormones on serum lipids and lipoproteins in humans, *Metabolism* **4:** 298–301, 1955.

TRENDS IN RESEARCH ON THE AGING NERVOUS SYSTEM*

CHARLES RUPP, M.D.†

Lankenau Hospital, Philadelphia, Pennsylvania

Numerous publications attest a broad research interest in many aspects of the aging nervous system during the past decade. Because of the magnitude and urgency of the problems resulting from the rapidly increasing extension of the life span with a concomitant increase in the number of individuals surviving to the later years of life, investigative interest has been predominantly at clinical levels. Basic biologic research in the fields of histopathology, histochemistry, pathophysiology, pathochemistry and metabolism, even if not entirely dormant, has not been commensurate. Although this trend is understandable, progress has been impeded since clinical investigations have often, of necessity, been based on empiricism rather than on basic biologic concepts.

NEUROHISTOPATHOLOGIC AND METABOLIC STUDIES

Let us first consider recent studies of the neurohistopathologic changes associated with aging of the nervous system. With aging there occur alterations in the structure of, and a diminution in the number of cortical neurones (1). The commonest change is in the Nissl substance, which stains palely, and becomes scattered through the cystoplasm (2). The cellular outlines are shrunken and irregular, the cystoplasm appears hypochromic, the nuclei become basophilic, and there is evidence of neuronophagia and glial proliferation. Changes are also found in the intercellular matrix and intracellular neurofibrils. Although such cellular changes are constantly present, they are not proportionate to chronologic age or to the duration or extent of clinical symptoms (3). Of interest are Andrew's findings (4) that the changes caused by aging are similar to those resulting from inanition.

Some investigators have attempted to correlate the changes of neuropathologic aging with metabolic dysfunctions. Stern and Elliott (5) subjected a group of rabbits to experimental dehydration in order to determine any correlation with the so called Alzheimer neurofibrillary changes. Histologic examination revealed that in some irregularly scattered neurones, the intracellular argyrophil fibers became coarse and showed a tendency to form matted strands, the nuclei appearing intact. Roizin (6) investigated the relation between morphologic and histometabolic changes in brain biopsies of 2 cases of presenile psychosis. He found that the indophenol and peroxidase reactions in the ganglion cells were either reduced in intensity, diminished or lacking. Some sections revealed marked chromatolysis, or the presence of lipid degenerative material. Other cells showed

* Read as part of a symposium on Stress and the Nervous System under the auspices of the American College of Physicians, at the Lankenau Hospital, Philadelphia, April 21, 1955.

† Chief, Department of Neurology and Psychiatry, Lankenau Hospital.
Office address: 133 South 36th Street, Philadelphia 4.

an increased reaction of the acid phosphatases, particularly those neurones with marked chromatolysis and peripheral displacement of the nucleus. Application of iron salts frequently disclosed changes in areas demonstrating altered indophenol and peroxidase reactions. Some markedly shrunken ganglion cells contained a few granules of calcium salts. Sosa (7) found changes in the neurofibrillary network occurring in relation to the accumulation of lipochrome (lipofuscin pigment). These alterations were observed with particular frequency in the nerve cells of normal old individuals and it was believed justifiable to consider them an aging process.

In metabolic studies using the Quick intravenous hippuric-acid test, Stern (8) found that the incidence of faulty detoxication was more than three times higher in psychotic patients, aged 60 years or older, than had been found by previous investigations in mentally normal patients of the same age group. However, a small number of senile dementia patients had low values even when compared with patients of the same age suffering from affective disorders or from hypertensive encephalopathy.

Other studies suggest that neuropathologic and metabolic changes are not the sole causes of the clinical symptoms of senile mental change. Simon and colleagues (9), using the level of lipoproteins to indicate atheroma formation, found evidence of no more arteriosclerotic activity in some 200 mental hospital patients than in normal patients of the same age. They concluded that cerebral arteriosclerosis plays only a small role in the production of clinical symptoms. Sands and Rothchild (10), from a comparative study of psychotic men aged 60 years or older, and 15 healthy volunteers, suggested that a combination of personality and somatic factors accounts for the development of severe cerebral arteriosclerotic symptoms, since the cerebral changes in many of the psychotic patients differed neither in kind nor degree from those found in the non-psychotic aged. They are of the opinion that personality factors are as important as local pathology in the production of clinical symptoms.

Bailey (11) studied the histologic changes associated with aging in the spinal cord. After the age of 30, the arteries and arterioles sometimes showed thickened walls and narrowed lumens. Occasional slight demyelination in the posterior part of the posterior columns, usually accompanied by gliosis, was noted in the sixth decade, at which time pigment atrophy of the ganglion cells first appeared. Corpora amylacea were noted as early as the fourth decade and were always present after the fifth. All changes were much more apparent and constant after the age of 60, but still were not severe. There was no positive correlation between the changes due to age and the degree of arteriosclerosis. Aging, like growth, appears to be a process inherent in the cell itself. It was difficult to correlate the observed changes with the patient's clinical condition.

Physiologic studies of the aging nervous system have been chiefly concerned with investigations of the cerebral circulation by the nitrous oxide technique of Schmidt and Kety. Freyhan and co-workers (12), utilizing this method, demonstrated that the senile psychoses are associated with a significant reduction in cerebral oxygen utilization on the basis of an increased cerebrovascular resistance

and a resultant significant reduction in cerebral blood flow. Findings in patients with psychoses due to arteriosclerosis were essentially the same. Fazekas *et al.* (13), investigating cerebral hemodynamics and oxygen consumption in subjects aged 50 or older, found that in the average elderly person, in spite of the absence of any clinical involvement of the nervous system, some degree of arteriosclerosis was manifested by an increased cerebrovascular resistance and a reduction in cerebral blood flow. Changes were more marked in elderly patients with clinical evidence of cerebrovascular disease, regardless of how the latter became manifest. The level of cerebral oxygen consumption in the elderly, with or without evidence of cerebrovascular disease, was significantly reduced but appeared to have little relationship to the clinical signs of vascular involvement. Inhalation of 10 per cent oxygen caused no over-all change in cerebral oxygen consumption. Inhalation of 5 per cent carbon dioxide caused an increase in cerebral blood flow similar to, but not as extensive as that reported for younger subjects. It was suggested that decreased cerebral enzyme activity and/or impaired oxygen availability may contribute to the changes in central nervous system function so frequently observed in the aged.

In further studies (14), the same investigators observed that in patients 50 years of age or older, with cerebral arteriosclerosis with or without hypertension, the administration of 5 per cent carbon dioxide, intravenous aminophylline or hyperventilation resulted in cerebral hemodynamic changes similar to those noted in younger subjects with no evidence of cerebrovascular disease. These findings suggest that, even in the presence of cerebral arteriosclerosis with or without hypertension, the cerebral vasculature is capable of at least a partial relaxation and, conversely, is sufficiently elastic to undergo a further increase of tone in response to appropriate stimuli.

Schemberg (15) confirmed that the cerebral blood flow is lower and the cerebrovascular resistance greater in normal middle-aged subjects than in normal young subjects. These trends progress with age, especially after the fiftieth year. The progressive reduction in blood flow appears related to the increase in cerebrovascular resistance, indicating a reduction in the vascular lumen due either to arteriosclerosis, an increase in tone, or both.

The effect of genetic factors in senescence is demonstrated by Kallman's (16) comparative study of twins. Whereas fraternal twins who have lived in the same environment often manifest different clinical courses in senescence, identical twins raised in different environments often consistently have the same types of disorders and pathologic conditions at the same time in life and in the same manner. The same author states (17) that theories of simple dominance or recessiveness are inconclusive when it comes to mental disorders peculiar to the senium, with the possible exception of some types of presenile brain atrophy. Apparently the etiology of the usual forms of senile psychosis is based on an interplay of complex determining factors, among which are age, susceptible personality traits, reduced adaptive plasticity, and those gene-specific biochemical phenomena which control growth or decline.

CLINICAL STUDIES

Attention has been given to many facets of the clinical problems associated with the aging nervous system. Time limitations prevent a detailed survey. Only the more important research trends will be mentioned.

Several investigators have attempted to determine the value of various drugs in the treatment of patients presenting psychiatric disorders associated with aging.

Garnett and Klingman (18) used cytochrome-C in 17 presenile, senile and arteriosclerotic patients and reported a resultant improvement in memory, mentation and behavior in 11 . They acknowledged that the chemical role of this enzyme is not well established. Forster and Bradford (19), however, found that there was no significant improvement in patients receiving cytochrome-C when compared to those receiving sterile saline injections.

Another drug which has had a more extensive clinical trial has been oral Metrazol, which is a central nervous system stimulant. It acts chiefly on the respiratory, vagal and vasomotor centers of the medulla, but also has a stimulating effect on all levels of the neuraxis. It is reported to deepen respiration, stimulate circulation, re-establish vascular tone and increase cerebral oxygen exchange.

Chesrow (20) gave from 1½ to 6 grains daily to 32 bedridden, confused aged patients with arteriosclerosis, for a minimum of ninety days. Beneficial effects were noted in 26, and were marked in 12. Fatigue and confusion were reduced, mood was elevated and there was improvement in mental and physical activity. Aside from nausea and vomiting in a few patients, there were no disturbing side effects. Jensen and Leiser (21) also reported moderate to marked improvement in approximately half of a group of 30 patients with cerebral arteriosclerosis. The drug appeared to exert its most profound effect on patients who had been unstable, asocial, disagreeable, untidy and often semi-stuporous. With treatment, they became more tractable and easy to care for. Although nausea and vomiting occurred in 9, this subsided when medication was discontinued for two days and did not recur when treatment was resumed at a lower dosage level.

Other investigators report variable results. Swenson and Grimes (22) found that, although there was some subjective improvement, comparison with a control group revealed no statistically significant differences. Mead *et al.* (23) likewise noted no significant improvement in 24 patients compared with a control group and concluded that Metrazol is without value. Gross and Finn (24a) stated that although 7 of 10 patients showed a slight improvement in memory, no patient improved enough to warrant discharge from the hospital, and some became more confused and deluded. Convulsions have been reported following oral administration of the drug (25), particularly in patients with a familial history of epilepsy or in whom the electroencephalogram revealed focal abnormalities. Further study will be necessary before final conclusions can be drawn regarding the usefulness of Metrazol.

Gregory (24b) reported favorable results with nicotinic acid in the psychoses of senility. The drug appeared to be of more benefit in prophylaxis than in cure.

Daily administration of small doses may prevent or delay the onset of some cases of senility.

Thorazine and the Rauwolfia compounds have been reported to be useful in controlling the severe anxiety and agitation which occurs in some senile and aged persons.

Recently, at the Lankenau Hospital, Bortz, King and Rupp have begun an investigation to determine the therapeutic potentialities of alpha,2-piperidyl,-benzhydrol hydrochloride (Meratran) in patients over 60 with sensorium disturbances, fatigue states and hypertensive encephalopathy. This drug is a central stimulant without autonomic side effects. It does not induce elevation in blood pressure or pulse rate, nor does it impair appetite or disturb sleep. It has some value as an antidepressant in reactive and endogenous depressions (26). It has also been useful in the treatment of blepharospasm, spasmodic torticollis and narcolepsy (27). Our own investigations have been underway for too brief a period to permit us to formulate even tentative conclusions.

We are cognizant that emotional factors are important in the etiology and therapy of the psychiatric disturbances of the elderly and the evaluation of any drug must be carefully controlled in an attempt to determine how much of the improvement can be attributed to the drug itself and how much arises from the attention, interest and broad psychotherapeutic effects accruing to the patient whose morale is elevated by the knowledge that an effort is being made to help him. Discussion of the importance of emotional and psychologic factors in the aged is beyond the scope of this study.

The therapeutic usefulness of stellate ganglion block in the treatment of the so-called cerebral thromboses has attracted much interest. After many intensive, well controlled trials, the general consensus now is that this procedure is essentially valueless and may even be dangerous (28).

Several studies have been concerned with the pathophysiologic mechanisms for the production of the cerebral infarcts, which are the more usual pathologic findings in cases of so-called cerebral thrombosis. Wilson and associates (29) found in a study of 542 cases that the past medical history, clinical examination or autopsy revealed evidence of cardiovascular insufficiency in 451 (83 per cent). These findings suggest that systemic circulatory inadequacy plays an important role in the causation of cerebrovascular accidents, and that preventive measures and therapy should be directed toward maintaining the general circulatory status at a maximum level. Hicks and Warren (30), however, believe that the ischemia which is the cause of cerebral infarction is most often due to cerebral vasospasm, less often to thrombosis and least frequently to systemic circulatory failure, embolism and arteriosclerosis. It is obvious that the final word has not been forthcoming.

Cerebrovascular disease and senile Parkinsonism rank high among the more frequently observed neurologic disorders of the aged. Several clinical studies indicate a vigorous interest in these and other less common neurologic afflictions. Many new drugs have been advocated as having varying degrees of usefulness in the therapy of Parkinsonism. Although further clinical trial is justified, the

results as yet have not indicated that any of these drugs possesses overwhelming advantages over the older medications such as hyoscine, atropine and Artane. No drug has any appreciable effect on the Parkinsonism tremor. Cooper (31) has recently advocated ligation of the anterior choroidal artery for relief of the rigidity and involuntary movements of Parkinsonism. Although it is too early for a definite evaluation of this procedure, results so far are inconclusive. Permanent hemiplegia has resulted in some cases, most likely because there is a good bit of individual variation in the areas supplied by the vessel.

Several studies (32, 33) call attention to the prevalence of primary brain tumors in aged persons. Accurate diagnosis is often difficult because of concomitant cardiovascular disease, and symptoms are attributed to the latter. Other factors contributing to delayed or erroneous diagnosis include severe mental deterioriation and predominant psychiatric symptomatology. Complete study is frequently omitted because of the disturbed mental state and the advanced age of the patient. From the pathologic standpoint, most brain tumors are gliomas of varying degrees of malignancy. Operative results are generally discouraging although, rarely, good results may be obtained if the tumor is benign.

Of interest are the recent studies (34, 35) on cervical spondylosis, a degenerative disorder involving the intervertebral disc. Aging seems to be the prime etiologic factor, since most of the patients are 50 years of age or older. Diminution of the water content of the discs progresses with age. Other contributing factors include wear-and-tear secondary to the free mobility of the cervical spine, congenital abnormalities, or prior trauma. Secondary to the disc degeneration, bony changes develop in the cervical vertebrae. Narrowing of the spinal canal results from various combinations of osteophytosis, subluxation of the cervical vertebrae and loss of cervical lordosis. Narrowing of the intervertebral foramina may result from osteoarthritis of the neuro-central and apophyseal joints. Fibrosis of root sleeves and vascular changes sometime occur. Narrowing of the spinal canal leads to signs of cord involvement, and foraminal narrowing can produce root involvement. Involvement of the spinal cord and nerve roots often occurs silently, with neurologic signs antedating development of symptoms. Root involvement may lead to muscle wasting, weakness and acroparesthesia, and periarticular adhesions about the shoulder joint. In the spinal cord, patchy demyelination with ascending and descending degeneration may result as well as myelomalacia in more severe cases. The syndrome of cervical myelopathy due to spondylosis can simulate motor neurone disease, multiple sclerosis, posterolateral sclerosis, primary lateral sclerosis and progressive paraplegia. The symptoms progress slowly over several years and then tend to remain stationary. The dynamics and composition of the cerebrospinal fluid are usually normal. Arrest of the pathologic changes is most likely to be accomplished by immobilization of the neck. Traction is of no value. Surgical decompression may be of benefit when the patient is relatively young, the duration of symptoms brief, the disc changes single rather than multiple, and when vascular changes are absent.

COMMENT

In spite of the extensive research interest in recent years, it is obvious that many gaps still exist in our knowledge of what actually happens as the nervous system grows old. Research expansion at basic levels should furnish fruitful leads for further investigation. Until such data become available, clinical studies can be helpful in resolving conflicting observations, and extending present knowledge. An intensive clinical investigation involving the comparison of a group of elderly patients relatively free of neurologic and psychiatric disabilities with a group having marked disabilities might well furnish several valuable clues. Nutritional and metabolic studies, at present all too neglected, should prove to be revealing. The roles of heredity and emotional stress need to be assessed in more detail.

In spite of present shortcomings, the problems which will arise as more and more people survive to the older years of life will focus attention even more vigorously upon the aging nervous system. Chances are bright that in the next decade many new truths will be revealed which will greatly expand our understanding, enrich our therapeutic potentialities, and alleviate the suffering of those who live long.

REFERENCES

1. O'Leary, J. L.: *in* Cowdry's Problems of Ageing, edited by A. C. Lansing. Baltimore, The Williams and Wilkins Co., edition 3, 1952, p. 223.
2. Rothschild, D.: Pathologic changes in senile psychoses, *Am. J. Psychiat.* **93:** 757, 1937.
3. Riese, W.: The cerebral changes in very old human brains, *J. Neuropath. & Exper. Neurol.* **5:** 160, 1946.
4. Andrews, W.: Neuronophagia in the brain of the mouse as a result of inanition and in the normal aging process, *J. Comp. Neurol.* **70:** 413, 1939.
5. Stern, K., and Elliott T. A.: Experimental observations on the so-called senile changes of intracellular neuro fibrils, *Am. J. Psychiat.* **105:** 96, 1948.
6. Roizin, L.: Histometabolic changes and neuropathologic selectivity in the light of recent investigations, *J. Neuropath. & Exper. Neurol.* **7:** 216, 1948.
7. Sosa, J. M.: Aging of neurofibrils, *J. Gerontol.* **7:** 191, 1952.
8. Stern, K.; Hinds, E. W., and Aslowa, B. A.: Aging and detoxication studies in hippuric acid synthesis during psychoses of involutional and old age groups, *Am. J. Psychiat.* **102:** 325, 1945.
9. Simon, A., and others: Lipoproteins in general and cerebral arteriosclerosis. Preliminary report, *Am. J. Psychiat.* **108:** 663, 1952.
10. Sands, S. L., and Rothschild, D.: Sociopsychiatric foundations for a theory of the reactions to aging, *J. Nerv. & Ment. Dis.* **116:** 233, 1952.
11. Bailey, A. A.: Changes with age in the spinal cord, *Arch. Neurol. & Psychiat.* **70:** 299, 309, 1953.
12. Freyhan, F.; Woodward, R., and Kety, S.: Cerebral blood flow and metabolism in psychoses of senility, *J. Nerv. & Ment. Dis.* **113:** 449, 1951.
13. Fazekas, J. F.; Alman, R. W., and Bessman, A. N.: Cerebral physiology of the aged, *Am. J. M. Sc.* **223:** 245, 1952.
14. Fazekas, J. F.; Bessman, A. N.; Cotsonas, N. T., and Alman, R. W.: Cerebral hemodynamics in cerebral arteriosclerosis, *J. Gerontol.* **8:** 137, 1953.
15. Scheinberg, P.; Blackburn, K.; Rich, M., and Saslaw, M.: Effects of aging on cerebral circulation and metabolism, *A.M.A. Arch. Neurol. & Psychiat.* **70:** 77, 1953.

16. Kallmann, F. G.: Genetic aspects of mental disorders in the aging; comparative twin data on involutional and senile periods of life, *J. Hered.* **43:** 89, 1952.
17. Kallmann, F.: The genetics of psychoses, *in* Res. Publ. Assn. Nerv. & Ment. Dis. Baltimore, The Williams & Wilkins Co., 1954, vol. 33, p. 363.
18. Garnett, R. W., and Klingman, W. O.: Cytochrome C: effects of intravenous administration in presenile, senile and arteriosclerotic cerebral states, *Am. J. Psychiat.* **106:** 697, 1950.
19. Forster, W., and Bradford, E. J. G.: Cytochrome C in senile and arteriosclerotic dementia, *J. Ment. Sc.* **97:** 718, 1951.
20. Chesrow, E. J.; Giacobe, A. J., and Wosika, P. H.: Metrazol in arteriosclerosis associated with senility, *Geriatrics* **6:** 319, 1951.
21. Jensen, E. H., and Leiser, R. The use of oral Metrazol in psychosis with cerebral arteriosclerosis, *J. Michigan M. Soc.* **52:** 734, 1953.
22. Swenson, W. M., and Grimes, B. P.: Oral use of Metrazol in senile patients, *Geriatrics* **8:** 99, 1953.
23. Mead, S.; Mueller, E. E.; Mason, E. P.; Kheim, T., and Kountz, W. B.: A study of the effects of oral administration of Metrazol in old individuals, *J. Gerontol.* **8:** 472, 1953.
24. (a) Gross, M., and Finn, M. H. P.: Oral Metrazol therapy in psychotic senile and arteriosclerotic patients, *J. Am. Geriatrics Soc.* **2:** 514, 1954.
(b) Gregory, I.: Nicotinic acid therapy in psychoses of senility, *Am. J. Psychiat.* **108:** 888, 1952.
25. Trevathan, R. D.: Convulsive seizures during oral pentylenetetrazol therapy, *Geriatrics* **9:** 489, 1954.
26. Fabing, H.: Clinical experience with Meratran, *Dis. Nerv. Syst.* **16:** 3, 1955.
27. Fabing, H.: Benzhydrol hydrochloride; a new central stimulant in the treatment of blepharospasm, spasmodic torticollis and narcolepsy, *Tr. Am. Neurol. A.* 1954, p. 159.
28. Millikan, C. H.; Lundy, J. S., and Smith, L. A.: Evaluation of stellate ganglion block for acute focal cerebral infarcts, *J. A. M. A.* **151:** 438, 1953.
29. Wilson, G.; Rupp, C.; Riggs, H. S., and Wilson, W. W.: Factors influencing the development of cerebral vascular accidents, *J. A. M. A.* **145:** 1227, 1951.
30. Hicks, S. P., and Warren, S.: Infarction of the brain without thrombosis, *A. M. A. Arch. Path.* **52:** 403, 1951.
31. Cooper, I. S.: Effect of anterior choroidal artery ligation on involuntary movements and rigidity, *Tr. Am. Neurol. A.* 1953, p. 6.
32. Pennybacker, J.: Intracranial tumours in the aged, *Edinburgh M. J.* **56:** 590, 1949.
33. Rupp, C.; Riggs, H. E.; Hogan, H. W., and Moulton, J. A.: Primary brain tumors in patients over age 60, *Neurology* **3:** 586, 1953.
34. Brain, R.: Cervical spondylosis, *Ann. Int. Med.* **41:** 439, 1954.
35. Pallis, C.; Jones, A. M., and Spillane, J. D.: Cervical spondylosis; incidence and implications, *Brain* **77:** 274, 1954.

ROENTGEN THERAPY OF CHRONIC CHEST SYMPTOMS IN THE ELDERLY*

ANTHONY F. ROSSITTO, M.D.†

Wichita Hospital, St. Joseph's Hospital, and Sedgwick County Hospital, Wichita, Kansas

In the older age group the more important chest symptoms which result in debility, exhaustion and general poor health are cough, severe and/or long-lasting pain, dyspnea and orthopnea. It is the purpose of this discussion to emphasize the use of roentgen therapy in the alleviation of these symptoms when caused by inflammatory conditions.

Roentgen therapy, in the past, has been recommended for the treatment of these symptoms only because all other methods failed. This does not speak against roentgen therapy; rather, it is a compliment. All results with this method cannot be explained scientifically. However, the benefits obtained have promoted dependence on the use of roentgen irradiation, even as an aid in the differential diagnosis of thoracic lesions.

ROENTGEN THERAPY OF COUGH

In the elderly, the most important chest symptom to control is cough. Cough may be present alone, or with dyspnea and pain, and may be of such severity as to promote debility or to initiate chest pain, dyspnea and orthopnea. It can be a serious symptom and demands treatment. In our experience, the most common causes of cough are unresolved pneumonia, fibrosis of the hilar, perihilar and medial lung areas (due to repeated attacks of so called "bronchitis"), and hilar and mediastinal chronic inflammatory adenopathy. Other less frequent pulmonary conditions are pulmonary emphysema, bronchiectasis, and the asthmatic syndrome (in which symptoms are made worse by recurrent infections). These last three conditions usually result in the so-called "geriatric pulmonary invalid." Aid is definitely needed by this group of patients, because cough decreases pulmonary ventilation—already embarrassed.

In all these pathologic conditions infection must be predominant in order that there be an effective response when roentgen therapy is administered. The modus operandi is the same as when infection occurring elsewhere in the body is subjected to roentgen therapy. The theory is that chronically infected tissue has an overabundance of lymphocytes, leucocytes and eosinophils. These cells are destroyed readily when subjected to small doses of x-irradiation, with resultant liberation of antibodies, ferments and other protective substances. Phagocytosis ensues or is increased, the debris and the bacteria are removed, and resolution

* Presented at the Annual Meeting of The American Geriatrics Society, New York, N. Y., April 21–22, 1955.

† Senior Radiologist at Wichita, St. Joseph's and Sedgwick County Hospitals; Consulting Radiologist, Wichita Veterans Hospital and Wichita Air Force Base Hospital, Wichita; Guest Faculty, University of Kansas School of Medicine, Kansas City, Kansas.

results. The rate at which this process proceeds in different stages of inflammation and infection corresponds to the rate at which these white blood cells are affected.

Children and elderly patients are more responsive than middle-aged or young patients. Since the dose is small, irradiation is administered twice weekly for two weeks and then at seven, ten or fourteen day intervals. Response is expected by the end of four treatments. A total of eight or ten treatments is given, by which time the cough is absent or is an insignificant symptom. If pulmonary fibrosis is the dominant pathologic feature, dyspnea and orthopnea accompany the cough. Consequently these symptoms must be relieved when the cough is controlled. This requires a second course of therapy or additional roentgen exposures given at two to four week intervals.

ROENTGEN THERAPY OF DYSPNEA

Dyspnea and orthopnea are not to be considered as irreversible symptoms just because fibrosis of the lungs, emphysema, bronchiectasis or pulmonary cysts are present. Many patients who have these pulmonary conditions have only mild dyspnea. After a severe strain is placed on the already existent pulmonary changes, with single or repeated attacks of acute infections in the lung, dyspnea and orthopnea become major symptoms of catastrophic character. The action of roentgen irradiation in alleviating these symptoms is based on the fact that it promotes resolution of the infection (either in the alveoli or interstices) and resorption of the fibrosis. This latter response permits some return of elasticity in the lung and consequently pulmonary ventilation is increased. Many of these dyspneic patients are labeled cardiac dyspneics, but they become symptom-free during roentgen therapy after the regimen of treatment for cardiac decompensation has failed. This would indicate that the diagnosis of cardiac dyspnea was incorrect. Hence, roentgen therapy acts as a method of differentiating the dyspnea caused by chronic pulmonary inflammatory changes from the dyspnea of chronic cardiac decompensation. When cough and dyspnea do not respond to therapeutic measures used for a decompensated heart, roentgen therapy should be tried. In pulmonary fibrosis, mild bronchiectasis, emphysema, or even when cystic changes are present, roentgen therapy should be tried for the same reasons.

Often sinus and post-nasal infection accompanies the pulmonary pathologic condition. If unresponsive to otolaryngologic treatments, roentgen therapy should be administered to the sinus areas. This necessitates re-arranging the treatment schedule so that the sinus treatments are given between dates of the chest treatments. One can expect a diminution in number or even complete absence of sinus attacks and chest colds, with a single course of roentgen therapy administered to those areas.

ROENTGEN THERAPY OF CHEST PAIN

Pain in the chest, whether of short or long duration, presents a more complicated problem in management because of the numerous etiologic factors. For simplicity, we mention only those conditions most frequently brought to our attention.

In pleurodynia, intercostal neuralgia and herpes zoster, relief of pain may be expected in practically all subjects. Roentgen therapy is administered to the chest over the areas of pain and over the dorsal spine, including a level higher than that of the pain segment. For this reason the lower cervical spine is sometimes included. Treatments are given at two or three day intervals, and a total of three or four usually suffice.

In pain from fibrositis and osteoarthritis with nerve-root syndrome, the entire length of the dorsal spine is irradiated. Four to eight treatments are given and the response is usually good.

With pain in the sternal and retrosternal area, with or without pain on swallowing, irradiation is administered to the mediastinum through anterior and posterior ports. The dosage is higher than usual, because the most common cause of the pain is chronic mediastinal inflammatory adenopathy. The plan here is to administer roentgen irradiation twice weekly for four treatments and then weekly and semi-monthly for an additional four to eight treatments.

The results are most beneficial in retrosternal pain and in herpes zoster, when fear, apprehension and exhaustion from pain are almost insurmountable. Results with the pain from fibrositis and arthritis in the spine and adjacent areas are equally satisfactory, and there is usually no necessity for further treatment.

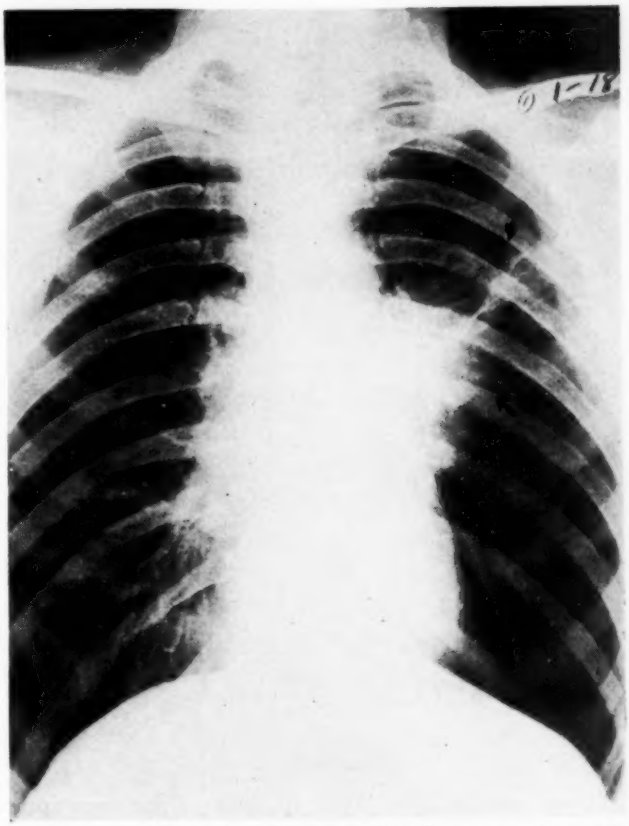

FIG. 1. Case 1 (January 18, 1954). Tumor and inflammatory densities involving left hilum, fixing corina. Severe and intractable cough with dyspnea.

CASE REPORTS

Case 1. Probable hilar tumor with chronic inflammatory changes

S-W., a man aged 65, had a severe cough and intractable dyspnea. His chest was very sore in the midline over manubrium. He had been ill for a considerable length of time and a diagnosis of pneumonia was made two days before hospital admission on January 17, 1954. Dyspnea had been present for four to five years, accompanied by chronic non-expectorant cough. Weakness due to cough caused the patient's retirement from work as an hotel operator.

Laboratory findings, including WBC, were normal. *A roentgenogram of the chest* showed a widened mediastinum with tumor density and inflammatory infiltration in the left hilum. Impression—tumor plus inflammatory changes (Fig. 1). *Bronchoscopy* revealed a fixed corina and left hilum. No tissue could be obtained and smears yielded negative results. A clinical diagnosis was made of inoperable carcinoma of the left bronchus.

An exploratory operation was refused by the patient, and he received daily x-ray treatments (from January 23 to February 3, 1954) through anterior and posterior mediastinal ports, each 1200 r.

Cough and dyspnea disappeared after about the fourth treatment and on March 30 the patient reported that he had no symptoms, was gaining strength and was working at times. On May 24, 1954 a film of the chest showed a completely resolved hilar lesion and a mediastinum narrowed almost to normal.

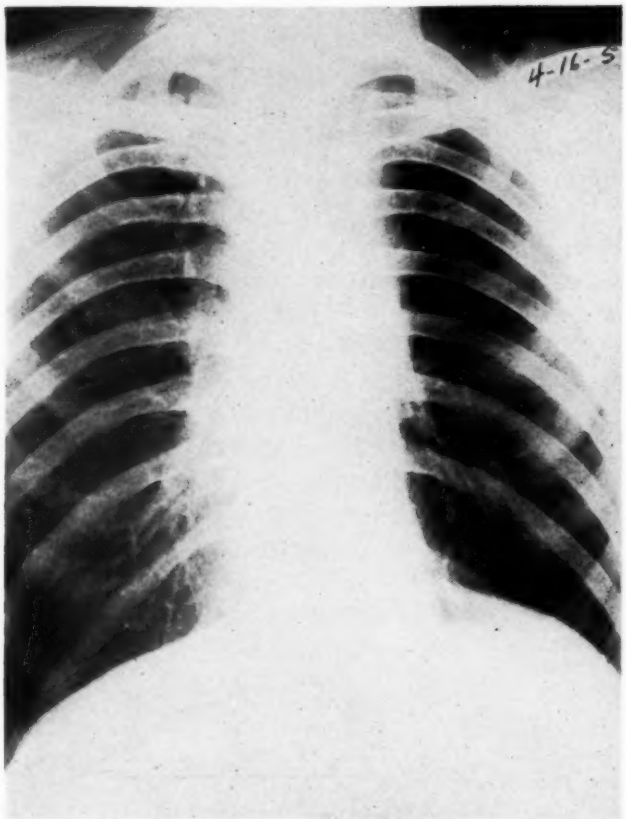

FIG. 2. Case 1 fifteen months later (April 16, 1955). Hilar area normal, with slightly widened mediastinum. Slight dyspnea was the only symptom.

On April 16, 1955 (Fig. 2) the mediastinum was slightly widened, but the left perihilar area was normal. The patient is back at work, with slight dyspnea, but feels well and happy. At the time of his last report in June 1955, one and a half years after irradiation treatment, he was relatively well.

Case 2. Unresolved inflammatory changes of pulmonary parenchyma

P-W., a woman aged 72, had severe cough, pain in left medial chest, copious expectoration and mild dyspnea. She had lost 8 pounds in two and a half weeks. Two months previously (about July 15, 1954) she had been considered very ill and had been told that she had a chest infection but no pneumonia. Since then she had been very weak and extremely tired all the time. She said she felt toxic and thought she had anemia.

She was an exhausted looking individual. Nothing abnormal was noted in her chest and throat.

Laboratory findings were normal. The WBC was 7,750, with a normal differential count. *A roentgenogram of the chest* on September 22, 1954 revealed a productive infiltration adjacent to the left border of the heart which suggested unresolved pneumonitis (Fig. 3).

The patient received five x-ray treatments (September 22, 24 and 27; October 1 and 11, 1954), each 100 r through the left lateral chest, with a posterior and anterior left chest treatment on the last date. By the third treatment her cough was practically absent but dyspnea was still present. Expectoration was very slight. By the fourth treatment she was feeling well and able to walk without tiring. Cough and expectoration showed further decreases

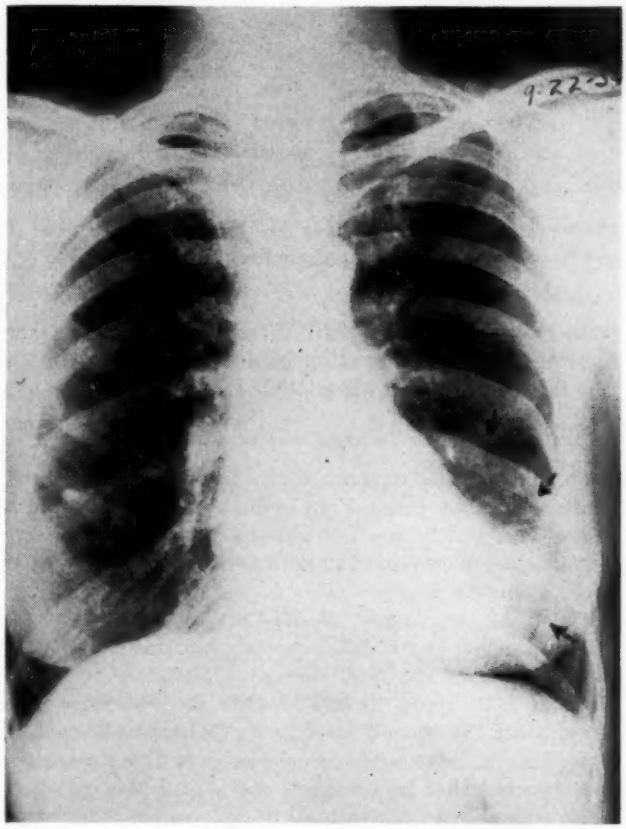

FIG. 3. Case 2 (September 22, 1954). Inflammatory infiltration (unresolved) in left base. Cough and expectoration, with mild dyspnea.

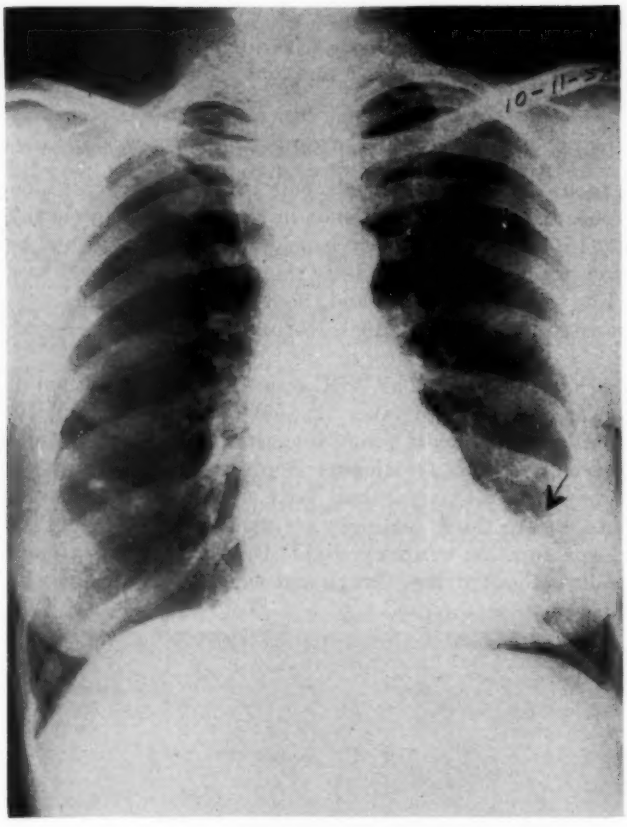

FIG. 4. Case 2 three weeks later (October 11, 1954). Considerable decrease in pneumonitis. Cough and expectoration practically absent.

and the patient looked well. On October 11, three weeks later, re-examination showed almost complete resolution of the infiltration in left chest (Fig. 4).

At the time of the last contact with the patient (February 18, 1955) she was normal.

Case 3. Chronic inflammatory fibrosis in hilar and perihilar regions

M-W., a man aged 61, had marked dyspnea with expectoration and extreme nervousness. He had had the dyspnea for many years. Four months before admission he had a pneumonitis; dyspnea became worse and he was not able to work as a bookkeeper. Weakness developed, with anorexia, a loss of 20 pounds, and a mild cough. There had been no response to ordinary measures, including antibiotics.

A roentgenogram of the chest on August 27, 1954 revealed fibrosis in the hili and medial lung fields, but no visible parenchymal inflammatory infiltration.

The patient received 100 r of roentgen therapy alternately to anterior and posterior chest fields on September 7, 10, 13, 16, 23 and 30, 1954. Response was rapid, and the cough was practically absent after the second treatment. There was almost no breathing difficulty by the last date. This patient received only six x-ray treatments. On April 13, 1955, six months later, he reported that he breathed easily and had regained the weight loss. Dyspnea was mild, he was able to perform all duties, and was living and working comfortably.

ROENTGEN THERAPY IN DIFFERENTIAL DIAGNOSIS

Only after all means have been used short of radical measures should roentgen therapy be instituted to help differentiate the following:

1. Primary lung, mediastinal and hilar tumors from chronic inflammatory pathologic lesions in corresponding areas.
2. Allergic from infectious conditions in the hili and perihilar areas.
3. Pulmonary interstitial fibrosis from chronic inflammatory pulmonary changes.
4. Chronic pulmonary inflammatory conditions from the appearance of the lungs in chronic decompensated heart disease.

Following small dosages of x-irradiation one can expect surprising and often rapid changes in symptoms and in chest roentgenograms in chronic inflammatory conditions, but no changes in the foregoing counterparts.

NOTES

The term chronic cardiac decompensation is used with the understanding that the roentgenogram shows an enlarged cardiac shadow and increased bronchovascular markings, with or without pulmonary edema.

Roentgen findings in pulmonary fibrosis due to chronic inflammatory conditions may show little or no change after roentgen therapy, although the symptoms of cough and dyspnea may disappear entirely, not to reappear until another pulmonic infection strikes.

So called "repeated attacks of bronchitis" usually represent exacerbations of a chronic inflammatory pulmonary process which has not resolved and which does not respond to the usual therapeutic measures. These attacks often cease after a course of roentgen therapy.

Most patients referred have had symptoms and roentgenographic changes for weeks to months, usually months. The results of x-ray therapy are not affected by the duration of the symptoms. Specific organic disorders (such as cardiovascular disease and tumors) which cause pain, cough and dyspnea, purposely have not been mentioned in this discussion.

The use of x-irradiation in the conditions discussed in this paper is not new. A considerable number of patients have been treated since 1937.

SUMMARY

Cough, pain, dyspnea and orthopnea are distressing and significant symptoms in the elderly.

Roentgen therapy, although usually used as a last resort when other therapeutic measures have failed, is effective in treating these symptoms.

The method is dependable, the course of treatment is relatively short, and repetition is usually unnecessary.

Because results are good even when used late, it is recommended the method be used earlier as the treatment of choice.

INTERDISCIPLINARY RESEARCH IN THE USE OF ORAL PENTYLENETETRAZOL (METRAZOL) IN THE EMOTIONAL DISORDERS OF THE AGED. STUDIES IN GERONTOLOGIC HUMAN RELATIONS. V.*†

MAURICE E. LINDEN, M.D.,** DOUGLAS COURTNEY, ED.D.‡ AND ALLAN O. HOWLAND, M.D.§

INTRODUCTION

One of the great developments in recent years has been the increase in interest and investigation into the needs of older mature patients. This group of people over the age of 65 who now number 13,500,000 and in three-quarters of a generation will approximate 22,000,000 have, until the last decade, been the victims of popular and scientific preconceptions. They have hitherto been thought of as having entered a biologic phase with organic physiologic decremental changes which are by their very nature irreversible. With this point of view as a premise, it has always been logical to regard the psychoses and behavioral alterations associated with cerebral arteriosclerosis and the senium as functions of a declining organism. Stemming from this principle, therapeutic neglect of the mentally-ill aged has been an appropriate method of management, provided it was at least accompanied by humane care.

In contrast today there is a growing realization among observers and investigators that the psychologic factor is a very significant one in contributing to the mental aberrations of the aged. Although the psychologic factor is far more promising than that of organic involution from the standpoint of therapeutic approach, it does not imply automatic reversibility. The question of the reversibility of psychologic functions depends upon: 1) knowledge of their origin, 2) emotional insight on the part of therapist and patient into their nature, 3) an incentive in both the treater and the treated to do something about them, and 4) a well-constituted setting with a therapeutic atmosphere conducive to the fulfillment of the patient's psychologic needs.

These elements apply generally to the treatment of emotional ills of all age groups but are especially important in gerontologic psychiatry, because for many therapists this requires a revision in thinking.

The reader is referred elsewhere (1, 2) for a more detailed excursion into the concepts of the psychoses of the senium. For the purpose of this paper it will suffice to point out that the psychologic disturbances of older people stem from three

* Read at the American Psychiatric Association annual meeting, St. Louis, Mo., May 7, 1954.

† This study was made at the Gerontologic Study Center, Norristown (Pa.) State Hospital. The planning, control and statistical handling were carried out at the Institute for Research in Human Relations, Philadelphia, Pa.

** Director, Division of Mental Health, Philadelphia Department of Public Health (Formerly Norristown (Pa.) State Hospital).

‡ Institute for Research in Human Relations, Philadelphia, Pa.

§ Norristown (Pa.) State Hospital.

sources: 1) life-long neurotic traits, 2) psychosexual recession, and 3) counter defensive attitudes in reaction to cultural rejection. The period of chronologic senility is a biologic and psychologic stage in the human life cycle. It is also a period of life characterized by social exclusion, individual isolation and neglect of the older mature person. These elements lead to the progressive development of what may be termed the *senile melancholic state*. The depressive character of the senile attitude thus generally promotes a feeling of insecurity, uselessness and loss of self confidence. Senile melancholy is marked by considerable anxiety and fearfulness which develop into a passively suicidal state. As a consequence of an intrapsychic massive upsurge of ego-shattering experiences, the aged patient tends to withdraw his libidinal energies and to concentrate them intrapsychically to repair injured defenses. The internalization of libidinal energies results in emotional isolation. In addition, the panic caused by crumbling defenses eventuates in psychophysiologic exhaustion. This is seen clinically as torpor, lassitude, waning alertness, memory impairment, confusion and disorientation. Concurrently, pathologic defenses become grotesquely elaborated into delusional transformations in efforts toward restitution. Finally, superimposed on this entire endopsychic process and pervading it, is the probable physiologic factor of cerebral ischemia (3, 4).

HYPOTHESIS

Levy's recent excellent summary (5) of the literature and research concerning the medical management of the aged outlines thoroughly the rationale lying at the basis of the use of an analeptic drug. The present authors are in substantial agreement with Levy's discussion.

An analeptic drug such as pentylenetetrazol (Metrazol®) appears to offer the following pharmacologic actions: 1) stimulation of the cerebro-spinal axis; Metrazol increases the transmission of nerve impulses and thus may behave as a general tonic-stimulant; 2) stimulation of cardio-vaso-respiratory and vagal centers; 3) indirect action through acceleration of circulation and improved pulmonary ventilation with an incidental increase in cerebral blood flow and oxygen supply; and 4) a possible physiologic effect of reduction in circulating lactic acid.

There is some evidence that part of the behavioral changes in the aged person may be a function of reduced oxygen in the blood supply to the brain. Metrazol would appear to have direct effects in counterbalancing the physiologic conditions present in the senile psychotic and cerebral arteriosclerotic patient. Since the action of the drug may set up a reciprocal set of improvements in both soma and psyche, each contributing to the other for a general total improvement, it is obviously imperative that any research concern itself not only with physiologic but also with general socio-psychologic (behavior) responses.

It seems clear, on the basis of experience with individual and group psychotherapy and a wide variety of activity programs (6–10), that in many instances the emotional problems of late maturity are wholly or partially resolvable, resulting in a return to better functioning. The key to the entire process is the

establishment of contact with the aged patient. Unfortunately, as a rule, such patients are found to have regressed to such advanced states of autistic withdrawal that contact is very difficult. The therapeutic need is a method of mobilizing mental energies and externalizing them, to the end that they may be channeled constructively and thus lead to the establishment of interpersonal relationships. It would be most desirable if a medication could be found which contains within itself the potential to induce two simultaneous effects: 1) improved oxygen supply to the hypoxic brain, and 2) liberated emotional energies for psychotherapeutic management. Metrazol would seem to lend itself to filling these needs.

Basing further efforts on the foregoing considerations, this group of researchers undertook an experiment to prove the efficacy of Metrazol in the in-patient treatment of the emotional aberrations of late and very late maturity. It was anticipated that, were the analeptic drug effective, it should succeed in eradicating feelings of depression and psychologic factors of confusion, and the following areas of behavior and feelings should be influenced: 1) feeling of well-being, 2) mood, 3) memory, 4) clarity of thought, 5) orientation, and 6) alertness. The prediction was made that changes in the foregoing mental activities could be observed objectively and recorded on multiple-point testing instruments so designed that changes in any direction could be rated over a time continuum.

METHODS

The observers

Since Metrazol is a dichotomous variable, having effects which are both psychologic and physiologic, the experiment was designed in such a way as to permit a great number of unbiased observations to be made by observers representing several different disciplines. The following observers were used: psychiatrist, clinical psychologist, research psychologist, statistical analyst, medical internist, laboratory pathologist, electro-encephalographer, psychiatric nurse, and the patient herself. Only the project director, who was the psychiatrist, knew the identities of the experimental and control patients.

Physiologic criteria

At the outset of this experiment much was already known about the pharmacologic action of Metrazol. Nevertheless, it was deemed advisable to perform certain laboratory studies before the administration of the drug and at regular intervals throughout the project in order to note whether any toxic factors were introduced by the drug. The following determinations were made at the beginning of the experiment, within two months after beginning administration of the drug, and at the end of the experimental period: complete blood count, levels of fasting blood sugar, total blood protein and blood urea nitrogen, icterus index, complete urinalysis, electroencephalogram, electrocardiogram and complete physical examination. Temperature, pulse, respiration, blood pressure and character of sleep were noted almost daily throughout the entire experiment. All of these data were collected in such a way that they could be analyzed statistically by an indifferent observer.

Selection of patients

The general patient population was a group of 330 aged women patients residing in a modern geriatric building of a state mental hospital. The ages ranged from 50 to 95, with a mean in the region of 73. The building was divided into halves and 170 patients and their records were carefully screened for diagnostic categories and for suitability for the experiment. One of the greatest problems encountered was that of selecting appropriate patients. It was the desire of this research team to find a representative group of aged female patients presenting characteristics of psychopathologic senescence and senility, in order to avoid as much as possible the treatment of psychotic patients who had grown old in the hospital. In this way it was felt that the patients sampled would more closely approximate the type of patient in the community for whom Metrazol therapy might be an appropriate treatment regimen. Surprisingly, it was discovered that of the 170 patients studied not more than 40 fulfilled the criteria of senile psychosis, simple senility, psychopathologic senescence or senile psychosis with arteriosclerosis. After further screening, using many interviews, a relatively pure population of 34 patients was selected. Thirty of these patients were arranged in rank order based on a clinical impression of the degree of preservation of most of their faculties. The odd-numbered patients were placed in the experimental group and the even-numbered in the control group. The only matching that was considered was mean age. The mean age of both experimental and control groups proved to be identical, 76.6 years. Reference to Table 1 will reveal that the two groups were nearly identical in all criterion areas.

Comparability of experimental and control samples

Although the selection of experimental and control samples was carefully executed to avoid the introduction of systematic bias, a further check was made

TABLE 1

Data on Comparability of Experimental and Control Samples

June 10, 1952

Variable	Experimental Values	Control Values	Significant Difference?
Sex	Female	Female	No
Age	76 yrs.	76 yrs.	No
Hemoglobin (Gm./100 ml.)	13.6	13.3	No
Blood sugar (mg./100 ml.)	105.3	111.9	No
Blood urea N (mg./100 ml.)	14.8	13.3	No
Blood protein (Gm./100 ml.)	7.93	8.30	No
Icterus index	6.7	7.3	No
Temperature (C.)	98.8°	99.1°	No
Pulse	78	73	No
Respiration	20	21	No
Blood pressure (syst.) (mm. Hg)	157	156	No
General behavior (nurses' obs.)	107.2	102.6	No
General behavior (psychiatrist's obs.)	82.2	79.4	No

of the comparability of the samples. Measures were carried out on a number of fundamental physiologic and psychologic variables after the selection of the two samples and prior to the beginning of the experimental period. In Table 1 the comparable mean values are given for thirteen of these variables. In addition, indication is provided concerning the presence or absence of a significant difference between the experimental and control groups with regard to each variable. Certain of the variables not included in this first comparability table were measured in terms of the relative change in values from the first administration to the subsequent administration, and hence offered no absolute measure for initial comparison. Separate treatment is offered for the Rorschach, Wechsler Memory Scale, and Bender Gestalt results.

From the data presented in Table 1 and the results of related studies the authors had a great deal of confidence that the experimental and control groups might well have been drawn from the same population, that no significant sample biases existed, and that any subsequent net differences between the control and experimental samples might be attributed to the experimental medication.

Administration of Metrazol

An early research study with Metrazol performed by Chesrow *et al.* (11) provided a valuable guide for the determination of dosage. All of the experimental patients were started on doses of 0.20 Gm. (3 gr.) four times daily. It was soon found that with the tablet form of the medication (used throughout this project) there was a tendency toward nausea. This was counteracted in some patients by the giving of milk or antacids. With other patients it was found expedient to diminish each dose while increasing the frequency of administration, *e.g.*, 1 tablet, 0.10 Gm. (1½ gr.) six times daily.

Since Metrazol was being investigated in aged patients in many places throughout the country and its mode of administration being tested in various combinations, the present authors chose to administer it with a vitamin combination and to measure the efficacy of Metrazol plus vitamins against that of vitamins alone. Thiamine chloride (20 mg.) and ascorbic acid (25 mg.) were given with each dose of Metrazol.

The patients in the experimental group received Metrazol plus vitamins. Those in the control group received vitamins alone. The drug combinations were so arranged that all of the patients, experimental and control, received the same number of tablets. In this way the research patients were unable to determine what part they played in the experiment. In addition, all of the medications were given by student nurses under the leadership of a nonparticipating nurse. The nurse-graders knew neither the treatment regimens nor the specific identities of the participating patients.

After the first nine months of drug administration the two research groups were reversed, the experimental subjects becoming the controls, and vice versa. This was done in order to increase the research population and to note the duration of the change effected by Metrazol. The present paper is concerned with the first nine months. Studies on the duration of the behavior change and cross validation of all areas of observation are intended for later publications.

Criteria and criterion measures

In order to measure the relative effect of the experimental variable as opposed to its absence, certain criterion measures had to be designed. For all of the psychologic variables there were appropriate measuring instruments, from the simple thermometer to the Wechsler Memory Scale. In the general area of psychologic response or that of social human behavior there was no single instrument available for use. Toward this end a set of behavioral indices or rating scales was constructed. These rating scales were designed to offer a check list to the nurse, physician, and other observers for the measurement of observed behavior.

Observed indices

The observational system reproduced here was the basic mode of measurement of behavioral change for all observers, except for the patient's self-evaluation. (The latter consisted of 10 incomplete sentences.)

An additional qualifying comment was made available in each block but is here reproduced only in the first.

OBSERVED INDICES OF PATIENT STATUS

Name:..... Case Number:.....
(last) (first)
Name of Observer*:..... Date of Observation:.....
Position of Observer:..... Hour of Observation:.....

* Directions to observer: For each of the following items check the choice available which best describes the patient you are observing. If you do not like the choices available for any area *make the best choice* and then, in the additional space provided, write any qualifying comment you wish to make. Please indicate Date and Hour of your observation.

AREA I. BEHAVIOR TOWARD INANIMATE OBJECTS	
1. *Furniture*	*Check Here*
1-a. Decorates tastefully	1-a. ....
1-b. Respects value and protects furniture	1-b. ....
1-c. Indifferent	1-c. ....
1-d. Untidy	1-d. ....
1-e. Destructive	1-e. ....
* Additional qualifying comment:.....	
2. *Clothing and Other Fomites*	
2-a. Takes pains with personal appearance	2-a. ....
2-b. Abides by dressing routines	2-b. ....
2-c. Untidy	2-c. ....
2-d. Destructive	2-d. ....
2-e. Denudative	2-e. ....
3. *Food and Feeding*	
3-a. Eats well—enjoys food	3-a. ....
3-b. Eats indifferently	3-b. ....
3-c. Requires supervision	3-c. ....
3-d. Requires assistance	3-d. ....
3-e. Force-fed	3-e. ....
AREA II. BEHAVIOR TOWARD PEOPLE	
4. *Self*	
4-a. Attentive to personal welfare	4-a. ....
4-b. Over-attentive to personal welfare	4-b. ....

4-c. Requires assistance with personal routines	4-c. ....
4-d. Injurious to self	4-d. ....
4-e. Suicidal	4-e. ....
5. *Other Patients*	
5-a. Organizes social activities	5-a. ....
5-b. Friendly	5-b. ....
5-c. Seclusive or indifferent	5-c. ....
5-d. Threatening and hostile	5-d. ....
5-e. Homicidal, assaultive	5-e. ....
6. *Ward Personnel*	
6-a. Actively cooperative	6-a. ....
6-b. Passively cooperative	6-b. ....
6-c. Passively uncooperative	6-c. ....
6-d. Resistive	6-d. ....
6-e. Assaultive	6-e. ....
7. *Visitors*	
7-a. Hospitable and entertaining	7-a. ....
7-b. Cordial	7-b. ....
7-c. Indifferent	7-c. ....
7-d. Quarrelsome	7-d. ....
7-e. Assaultive	7-e. ....
AREA III. FEELINGS AND ATTITUDES	
8. *Predominant Mood*	
8-a. Cheerful (Elation)	8-a. ....
8-b. Euphoric (Elation)	8-b. ....
8-c. Exhilarated (Elation)	8-c. ....
8-d. Elated (Elation)	8-d. ....
8-e. Ecstatic (Elation)	8-e. ....
8-f. No perceptible mood (Indifference)	8-f. ....
8-g. Profoundly melancholic (Depression)	8-g. ....
8-h. Moderately depressed (Depression)	8-h. ....
8-i. Fearful (Depression)	8-i. ....
8-j. Anxious and/or apprehensive (Depression)	8-j. ....
8-k. Pleasant (Depression)	8-k. ....
8-l. Mild (Hostility)	8-l. ....
8-m. Sardonic (Hostility)	8-m. ....
8-n. Bitter (Hostility)	8-n. ....
8-o. Angry (Hostility)	8-o. ....
8-p. Enraged (Hostility)	8-p. ....
9. *Emotional Tone*	
9-a. Intense interest-enthusiasm	9-a. ....
9-b. Serious	9-b. ....
9-c. Superficial	9-c. ....
9-d. Indifferent	9-d. ....
9-e. Inappropriate	9-e. ....
10. *Toward Hospital Situation*	
10-a. Accepts institution and its purposes	10-a. ....
10-b. Prefers institution to outside adjustment	10-b. ....
10-c. Passively compliant	10-c. ....
10-d. Desires premature discharge	10-d. ....
10-e. Openly hostile or tends to elope	10-e. ....

11. *Toward Other Patients*
    - 11-a. Respects others' needs 11-a. ....
    - 11-b. Comprehends others' illnesses 11-b. ....
    - 11-c. Indifferent 11-c. ....
    - 11-d. Reacts to psychotic thinking of others 11-d. ....
    - 11-e. Hostile, quarrelsome 11-e. ....
12. *Toward Personnel*
    - 12-a. Warmly friendly 12-a. ....
    - 12-b. Respects personnel's duties 12-b. ....
    - 12-c. Passively compliant 12-c. ....
    - 12-d. Rejecting and negativistic 12-d. ....
    - 12-e. Dangerously hostile 12-e. ....
13. *Toward Own Illness*
    - 13-a. Able to compare illness with normal state 13-a. ....
    - 13-b. Realizes need for institutionalization 13-b. ....
    - 13-c. Uncertain about mental state 13-c. ....
    - 13-d. Too perplexed to evaluate 13-d. ....
    - 13-e. Regards illness as normal 13-e. ....

AREA IV. THOUGHT PROCESSES

14. *Initiation of Thought*
    - 14-a. Spontaneous 14-a. ....
    - 14-b. Conversational 14-b. ....
    - 14-c. Responsive when pressed 14-c. ....
    - 14-d. Relatively unresponsive 14-d. ....
    - 14-e. Negativistic or mute 14-e. ....
15. *Development of Thought*
    - 15-a. Attains goal idea readily 15-a. ....
    - 15-b. Circumstantial, but usually reaches goal idea 15-b. ....
    - 15-c. Remotely relevant — occasionally reaches goal idea 15-c. ....
    - 15-d. Irrelevant 15-d. ....
    - 15-e. Incomprehensible 15-e. ....
16. *Character of Thought*
    - 16-a. Expressive and original 16-a. ....
    - 16-b. Coherent 16-b. ....
    - 16-c. Partially understandable 16-c. ....
    - 16-d. Inappropriate 16-d. ....
    - 16-e. Garbled or disorganized 16-e. ....
17. *Content of Thought*
    - 17-a. Conventional 17-a. ....
    - 17-b. Complaining 17-b. ....
    - 17-c. Expresses delusions on deep questioning 17-c. ....
    - 17-d. Actively delusional without provocation 17-d. ....
    - 17-e. Irrational 17-e. ....
18. *Accuracy of Thought*
    - 18-a. Factual 18-a. ....
    - 18-b. Fabricates occasionally 18-b. ....
    - 18-c. Confabulates when forgetful 18-c. ....
    - 18-d. Actively phantasizes 18-d. ....
    - 18-e. Totally unreliable 18-e. ....

19. *Socialization of Thought*
- 19-a. Considerate and sensitive 19-a. ....
- 19-b. Teasing and chiding 19-b. ....
- 19-c. Vulgar on strong provocation 19-c. ....
- 19-d. Vulgar on slight provocation 19-d. ....
- 19-e. Continuously vulgar and obscene 19-e. ....

AREA V. PRESENT CONTACT WITH ENVIRONMENT

20. *Time*
- 20-a. Fully oriented 20-a. ....
- 20-b. Knows only essential time and dates 20-b. ....
- 20-c. Knows month 20-c. ....
- 20-d. Knows season or year 20-d. ....
- 20-e. No idea of time, date, or season 20-e. ....

21. *Place*
- 21-a. Fully oriented 21-a. ....
- 21-b. Knows home address, ward, and institution 21-b. ....
- 21-c. Knows only approximate locality of institution within 100 miles 21-c. ....
- 21-d. Knows only state or country 21-d. ....
- 21-e. Disoriented, agrees with suggestions 21-e. ....

22. *Person*
- 22-a. Fully oriented 22-a. ....
- 22-b. Identifies self and close associates 22-b. ....
- 22-c. Identifies self—uncertain re close associates 22-c. ....
- 22-d. Cannot recognize most associates 22-d. ....
- 22-e. Misidentifies and substitutes identities 22-e. ....

23. *Attention*
- 23-a. Alert and appropriate to situation 23-a. ....
- 23-b. Attention readily gained, but overly tenacious 23-b. ....
- 23-c. Attention easily gained, but overly distractable 23-c. ....
- 23-d. Obtained with some difficulty—partially preoccupied 23-d. ....
- 23-e. Unobtainable—preoccupied with internal stimuli 23-e. ....

AREA VI. PERCEPTIONS
- 24-a. Conventional 24-a. ....
- 24-b. Occasional uncertainty 24-b. ....
- 24-c. Misperceives (illusions) 24-c. ....
- 24-d. Occasionally hallucinates (specify sensory system) 24-d. ....
- 24-e. Actively hallucinates (specify sensory system—auditory, visual, olfactory, gustatory, tactile) 24-e. ....

AREA VII. MEMORY
- 25-a. Wealth of accurate information, past and present, equal to capacities 25-a. ....
- 25-b. Amnesia mainly for acute psychotic event 25-b. ....
- 25-c. Spotty memory loss 25-c. ....
- 25-d. Retention unreliable for present—fair for past 25-d. ....
- 25-e. Gross disturbance past and present 25-e. ....

AREA VIII. ATTITUDES TOWARD ACTIVITIES

26. *Entertainment and Recreation*

26-a. Spontaneous, organizes groups, encourages others to join	26-a. ....
26-b. Seeks ward entertainment (Radio, TV, special programs)	26-b. ....
26-c. Requires encouragement to join activities	26-c. ....
26-d. Indifferent and passive	26-d. ....
26-e. Shuns entertainments	26-e. ....

27. *Occupational Therapy and Rehabilitation*

27-a. Productive and spontaneous—proud of own and other's creations	27-a. ....
27-b. Interested in scheduled periods of creative work	27-b. ....
27-c. Sporadic attendance—unconcerned with flaws	27-c. ....
27-d. Restless activity or poorly directed productiveness	27-d. ....
27-e. Uninterested and unproductive	27-e. ....

28. *Privileges*

28-a. Has, and discharges discreetly, all privileges	28-a. ....
28-b. Uses partial privileges with discretion	28-b. ....
28-c. Supervised out-of-ward privileges	28-c. ....
28-d. Has freedom of part of building only	28-d. ....
28-e. Maintained in locked ward or isolation	28-e. ....

AREA IX. SUMMARY EVALUATION BY THE OBSERVER

Statement as to patient's attitudes in general, hospital adjustment, specific psychologic characteristics, areas of change or improvement, problems of management, and evaluator's own experiences with patient.

For each variable a reading was taken during a base period just prior to the experimental stage (June 10, 1952), and an additional reading was taken toward the end of the first experimental period. The complexity of the test and the ever-present limitations on available professional time did not allow these repeat readings to be taken on a single date, so the measurement of each variable represents a somewhat different time period. These readings, however, are called final readings.

The beginning and final readings were then compared for each variable in the experimental sample and compared for each variable in the control sample. The result represented the amount of change for each variable in both experimental and control groups. Then the amount of change in the control group was subtracted from the amount of change in the experimental group, to arrive at a net change for the experimental group. The amount of this change was recorded and the direction was recorded. Then the chance probability that these net mean changes would occur was determined and the result was placed against a predetermined significant point of 5 per cent.

For presentation and rational purposes the physiologic variables were separated from the psychologic variables.

The physiologic variables—for example hemoglobin, or blood sugar level—

TABLE 2

Net Mean Physiologic Changes Between Experimental and Control Samples

Variable	Nature of Change	Significant ??
	First 2–3 mos.	
Hemoglobin	Control values decreased .1 Gm. more than exper. values	No
Blood sugar	Control values decreased 11.8 mg. more than exper. values	No
Blood urea N	Experimental values increased .2 mg. more than control values	No
Blood protein	Experimental values increased; controls values decreased; net—.69 Gm.	No
Icterus index	Experimental values increased .83 more than control values	No
	First 6 months	
Temperature	Experimental values increased .1°; control values decreased .25°.	No
Pulse	Control values increased 2.6 per min. more than exper. values	No
Respiration	Control values increased .15 per min. more than exper. values	No
Blood pressure (sys.)	Control values decreased 2.6 mm. more than exper. values	No

were considered as criteria for the detection of toxicity in the experimental medication. If toxicity were to be manifested as a result of the experimental medication, it was felt that such manifestation would occur early in the experimental period. Hence readings were taken among certain physiologic variables over the first two or three months, and among certain other physiologic variables over the first six months, in order to determine the significance of the change. These data are presented in Table 2. It is clear that there were no significant net changes between the experimental and control samples along the lines of these fundamental physiologic variables. Thus the drug, administered according to this experimental design, appears nontoxic. Side effects and the clinical responses to the medication are discussed in a subsequent section of this paper.

The psychologic variables were measured over the entire experimental period and the net changes and their significances are indicated in Table 3. The only measure in this table that reaches the 5 per cent significance point is the psychiatric observation involving the use of the behavioral indices. Since the psychiatric observer in this case was the attending physician and one of the authors, and hence the only person knowing the identity of the experimental subjects, there is a possibility of unconscious observer bias (see subsequent discussion of clinical findings).

The reader will note, however, that although only one measure achieved the predetermined significance point, many of the measures indicated a change in the predicted direction. If we could assume that the methods used were measuring variables not correlated with each other, this disproportionate trend in the desired direction would be very significant. However, we cannot make the assump-

TABLE 3

Net Mean Psychologic Change Between Experimental and Control Samples

Variable	Nature of Change	Significant?	Predicted Direction
General Behavior			
Nurse observer	Experimental improved 7.6 points over C.	No	Yes
Psychiatrist observer	Experimental improved 15.2 points over C.	Yes	Yes
Wechsler Memory Scale			
Personal and current information	Net experimental improvment	No	Yes
Orientation	" " "	No	Yes
Mental control	" " "	No	Yes
Logical memory	" " "	No	Yes
Digit retention	" " "	No	Yes
Visual reproduction	" " "	No	Yes
Associative learning	" " "	No	Yes
Full scale	" " "	No	Yes
Rorschach			
Total responses	Net experimental decrement	No	No
Average time	" " "	No	Yes
Total F%	" " "	No	Yes
F—%	" " "	No	Yes
Sum C%	" " "	No	No
# of P%	Net experimental improvement	No	Yes
# of A%	" " "	No	Yes
Confabulations	" " decrement	No	Yes
# of M%	" " increase	No	Yes
General integrative evaluation	" "	No	Yes
Bender Gestalt			
Form	Net experimental improvement	No	Yes
Time	" " "	No	No

tion of non-intercorrelation among the variables measured, but the trend is provocative and is supported by clinical observations.

The psychometric criteria

The use of psychologic measures with very aged patients does not offer extensive norms, nor are the measures themselves especially adapted to older people. Thus the interpretation of data gained from these procedures is neither clear nor uncomplicated.

The variables in which the 5 per cent point of significance was approached are Personal and Current Information (Wechsler Memory Scale), General Integrative Evaluation (Rorschach), and Time (Bender Gestalt). Time, however, was not significant in the predicted direction. It was expected that less time would be consumed in reproducing the Gestalt designs in the group while the patients were undergoing experimental medication. Actually more time was consumed. What this means interpretatively is a matter of conjecture. It may mean a slowing

down of visual motor coordinative abilities due to the drug itself, which seems unlikely in light of the tendency toward improved quality. It could mean that the individual had become more interested—in a sense more conscientious in her approach to the test and was more concerned with perfecting of the gestalts regardless of time. In respect to the near-significant changes with the other two tests (Personal and Current Information of the Wechsler and General Integrative Evaluation of the Rorschach), it is interesting that the findings (though not reaching the acceptable standard for significant improvement) showed a tendency, at least, toward appreciable change. The general integrative analysis of the various individual Rorschach profiles seems a better approach than quantitative appraisals of individual and isolated Rorschach features and determinants—and in this case appeared to show a positive change. This suggests that, in general, the personality factors showed an improvement. That heightened interest in self and surroundings may then follow is suggested by the inclination of Personal and Current Information to become better and show amplification. Of considerable interest is the fact that these happen to be the more nonintellective of the various tests.

One of the outstanding findings noted on the Wechsler Memory Scale and the Bender Gestalt test was the almost universal difficulty encountered in handling of visual-motor material. The simple copying of gestalt figures called forth strained, and in many cases fruitless, efforts. When memory was required in addition, the task seemed even more insurmountable and resulted in predominant failure.

Difficulties in testing the geriatric group

The whole question of structured test situations at this chronologic age and for this particular psychiatric category is a provocative one. The examiner was confronted with considerable reluctance, resistance, and even rejection on the part of many of the patients. Even when there was compliant cooperation it was evident that fear and hesitancy to accept the challenge of this new and somewhat threatening situation were present. Almost all the patients were acutely aware of, and sensitive to the inadequacies arising from their age and their illness. Being confronted with tangible testing devices designed to articulate and challenge, constituted an uneasy experience, despite all that was done to promote a comfortable testing situation. This fear of insult to intellectual efficiency is a real one to those most vulnerable. In the future construction of psychologic devices for this age group it would seem appropriate to give this factor special attention.

The results are sufficiently challenging to observe that although only one of the net changes achieved the predetermined level of significance, they fulfilled somewhat less demanding requirements in the favorable direction. This gives us some reason to believe that Metrazol plus vitamin therapy as opposed to vitamin therapy alone shows promise in the treatment of senile women. In the section on clinical findings this promise will be discussed. When the clinical findings indicate that certain senile women in our experimental population seem to have benefited especially from the medication given in this research, we hope

eventually to determine what there is about these individuals that especially indicates the administration of Metrazol. These findings, then, in hypothetical form will be available for subsequent experimental tests, through a delimitation of our population to these types of aged women.

RESULTS

Significance of physiologic data

Blood studies. In general there was no statistically or clinically significant change throughout the entire experiment in the levels of fasting blood glucose, blood urea nitrogen (BUN) and total protein, or in the icterus index. The slight increases or decreases found in these indicators were readily ascribable to laboratory variation. Of some importance were the blood hemoglobin measurements, summarized as follows:

Blood hemoglobin

Experimental group (15 subjects)			Control group (14 subjects)		
Improved	Static	Decreased	Improved	Static	Decreased
6	6	3	3	3	8

In this criterion the value of 11 Gm. was regarded as the lower limit of normal. When hemoglobin readings of 15 Gm. or above were found, they were almost invariably accompanied by red blood cell counts of well over 4.5 million and were regarded as evidence of hemoconcentration. (Pulmonic valvulitis was ruled out.) The 3 patients in the experimental group who experienced a decrease in hemoglobin thus actually improved. In the control group, among the 8 whose hemoglobin decreased, 6 showed a critical low value in the neighborhood of 11 Gm., in spite of a prolonged high dosage vitamin intake. The "static" cases were in the normal range throughout the experiment.

The project was not set up with objective nutritional intake studies as one of the criteria, because of the realistic nursing problem involved. However, ward observers reported that the patients whose hemoglobin levels improved, also ate better and gained weight.

There were no significant shifts in red or white blood cell morphology nor in the proportions of cell types.

Urinalysis. Results of all of the urine subtests remained normal or static with the exception of that for albumin. In 7 of the experimental (Metrazol) patients and in 3 of the controls (vitamins alone), traces or very faint traces of albumin developed. In most instances the albumin was accompanied by red and white blood cells and bacteria, but not by renal cells. Since cystitis and prolapsus of various organs through the pelvic diaphragm are common in this age group and since the albumin cleared with urinary antiseptics, it was felt that this development was probably not due to introduced renal damage. Still, the high incidence of this complication in the Metrazol-taking group remains unexplained.

Electrocardiogram. EKG findings remained essentially unchanged in the entire project population.

Temperature, pulse, respiration and B.P. No significant changes in tempera-

ture, pulse, or respiration were found. Statistically the blood pressure readings remained unchanged, since their significance was measured by averaging. The large amount of data in this area is still being studied, but clinical observation suggests that in a sizable number of experimental cases undesirably high blood pressure was reduced by 20 to 50 mm. (of mercury) and sustained at the lower level.

Electroencephalogram. The extremely complicated problem of evaluating the numerous electroencephalograms is being reserved for a later publication. Out of the 68 EEG readings taken during this study, 39 showed cortical irritability. An unpredicted result was improvement of some of the EEG configurations. This occurred in 3 of the experimental group and in 2 of the control group. Of interest is the fact that the 3 experimental subjects whose EEG's improved were also the most markedly improved clinically. Of the 2 control patients whose EEG's showed gross improvement during vitamin therapy alone, one died of a known cardiac ailment and the other went home, although clinically unimproved.

Sleep. Objective scoring methods failed to show any observable changes in sleep habits. However, the spontaneous statements by patients regarding their sleep were significant. When it is remembered that these patients had no idea what they were getting or why, it is interesting that 9 of the group receiving Metrazol reported marked improvement in the character and quantity of sleep. Such statements as, "I don't know what you're giving me, but I haven't slept so well in years," were common. Two of the experimental patients on leaving the hospital insisted on taking along a supply of Metrazol and vitamin tablets. Improvement in sleep was less striking among the control patients but did occur.

Physical examination. Complete examinations were performed by the internist, who also filled out on each patient a form made up of 21 of the observed indices previously listed. He reported improvement in robustness, appearance, pallor, and alertness—more striking in the experimental group. In other respects the physical condition did not change, with the exception of a slight increase in enfeeblement in several of the control patients.

Clinical psychiatric observation

The psychiatric alterations were much more striking than indicated by the statistical analysis presented earlier. The general clinical estimate, including the number of patients sufficiently improved to be released from the hospital, is shown in Table 4.

Alertness and environmental contact improved in both groups, but the improvement seemed more marked in the patients receiving Metrazol. The increased activity, enthusiasm, and personal appearance of those receiving the analeptic drug were a refreshing observation. Some patients complained of jitteriness and excitement when taking Metrazol, but this condition was soon remedied by channeling the newly liberated energy into social, creative and psychotherapeutic activities. Some patients described a lightheaded and "drunk" feeling during Metrazol therapy. (This was especially found with a group of patients not in this project who received the elixir form of the drug.) The experi-

TABLE 4

Psychiatric Improvement Clinically Perceived

Number of Patients	Experimental Group (15 subjects)	Control Group (14 subjects)
Released or able to leave hospital	9	3
Much improved	10	3
Slightly improved	3	2
Same or worse	2	9
Enabled to start group psychotherapy program	6	2

mental group showed increased affability and a heightened interest in conversation.

One patient, F.R., was an outstanding example of improvement with Metrazol plus vitamins. She was a 75-year-old widow, hospitalized for twelve years before the administration of Metrazol. For years she had been in a bitter, hostile, passively suicidal rut depression, and was seclusive and irritable. Her isolation was enforced by her self-recriminations. Inconsolably vituperative and hotly sarcastic, she had receded into an utterly empty institutional life, merely waiting and hoping for death. Severely limited by osteoarthritis and weight loss she hobbled short distances for fundamental biologic routines. She had not been seen to smile in twelve years. When this patient had been under the Metrazol regimen for about two months, she was sufficiently alert and hungry for social contact to enable her to be coerced into attending group psychotherapy meetings. There she manifested a pseudo-rejecting transference (12) and in a few months became a fairly pleasant, jocular, teasing, and charming participant. At a party she asked to kiss the therapist and danced with him. Thereafter she gained weight, was much more agile and became a leading raconteur in patient gatherings. During the following months she obviously enjoyed life and friendships. Her death due to a long-standing cardiac condition was preceded by a tranquillity and good humor that she had not known for a sixth of her life.

Usually, improvement in general behavior took place in the first thirty days of drug administration. Still, a fair number of patients did not show marked change until they had been on the medication for six to eight weeks, and sometimes longer.

Some of the patients complained about being harnessed to a multiple pill-taking routine, but as a rule the medicine was not refused. One paranoid woman who refused from the outset to take any pills was dropped from the experiment.

INTERPRETATION OF FINDINGS

The moderate discrepancy between the lack of significance on statistical analysis and the clinical estimates of improvement can be accounted for on at least the following bases: 1) Statistics treat of blocs of people, with the result that areas of change in a positive direction and areas of change in a negative direction tend to cancel each other out and do not show up numerically. 2) Data

of the type amassed in this study should be minutely examined, with special weighting being given to particularly important areas of observation (now being carried out with these data). 3) Refined as testing instruments may be, they are nonetheless gross as compared with clinical acumen and the numberless intuitive observations for which words do not exist.

The third point just mentioned is borne out by a study of the psychologic tests used in this experiment. The final numerical results of performance for the most part showed a trend in the predicted directions, and a few changes approached the point of significance. These were tests not having to do primarily with intellective functions, but rather with certain personality changes. It is thus seen that the Personal and Current Information on the Wechsler Scale was increased, reflecting greater interest in the self and surroundings. The General Integrated Evaluation of the Rorschach supported this finding, showing an all round improvement. The prolonged time factor of the Bender Gestalt may be thought of as further suggesting a greater interest and seriousness with regard to the individual and her behavior. This is probably the logical explanation of the Bender results, since in this study "prolonged time" was seen not to be an organicity factor. It seems, therefore, important and more than a coincidence that the results of tests which particularly involved the personality itself tended above all others in the direction of greater improvement.

There was universal improvement in the total project population. The vitamins played a part in this, because it is well known that this age group of patients tends on the whole to subsist on sub-standard diets. But this could not have been a very important factor because, although vitamin therapy was common to both groups, the experimental subjects improved much more than the control subjects, and because the physiologic response to vitamins was not reflected noticeably in the control group. It is likely that the main factors contributing to universality of response were the element of suggestion inherent in the giving of medicine and the supportive psychotherapy contained in the increased interest and attention expended toward these patients.

The large number of observers in this experiment, although increasing the soundness of the research, tended also to increase enormously its complexity. This report is a preliminary draft. Several divisions and correlations of this study have yet to be completed. Still the reader will note a trend toward agreement among all the observers, which increases confidence in the value of the experimental variable, Metrazol.

An interesting sidelight in this study was the effect the research had on the investigators themselves. The internist, who customarily was concerned with the noting of physiologic criteria which have relatively finite limits, found that the filling out of a psychiatric questionnaire required much effort, careful study, and intense self-searching. He commented that he had never before realized how exacting psychiatric observations must be, and that his respect for psychiatry reached a new high. He also stated that his part in the research sharpened his observations and gave him a new appreciation of "the emotional side of the patient."

The nurse-graders who had already had psychiatric courses and much practical work with patients, found that the Observed Indices form was virtually a mental examination and that their participation gave them a more precise, more realistic comprehension of patients' needs. Subsequently, reports on patients by these nurses became extremely valuable critical estimates and descriptions which tended to pin-point psychopathology, thus aiding the attendant physician immeasurably. This was also reflected in their improved ability to teach and supervise student nurses.

There can be no question but that research which requires the regular giving of medication, diagnostic procedures, examination of patients, and frequently changing interview situations is in itself an activator and a therapeutic factor in these patients. This must account for some of the improvement. Obviously anything that increases personal relationships with psychiatric patients who, as a rule, are lonely, frightened and unloved, will be beneficial. This alone makes thoroughly designed research worthwhile. The Metrazol appears, however, to have promoted a favorable change above and beyond this factor.

One additional point should be made here relative to the improved blood hemoglobin readings in the experimental patients. This is more apt to be a reflection of total improvement with better habits of nutrition, than a direct action of Metrazol.

CONCLUSIONS

A statistical and clinical study of the effects of sustained administration of oral Metrazol (13) on selected cases of the emotional disorders of late and very late maturity reveals that this drug is useful in improving patient well-being and helping to reverse many of the psychologic factors of chronologic senility that are reversible.

One point cannot be emphasized too strongly; no medication or system of treatment can be of much value if it is administered in an emotional vacuum. Neither Metrazol nor anything else known to this team will of itself induce spectacular benefits in the psychoses of senility. The stimulating effect of this analeptic drug makes energy available which must be channeled into a well designed program of activity, occupation, socialization, recreation and psychotherapy, if pronounced and demonstrable results are to be achieved. In other words, a philosophy of care of the aged must accompany any therapy containing at its core a method of tampering with somatic physiology.

Finally, it is fair to state that oral Metrazol is a safe medication which, even when administered in proper dosage for many months, does not adversely affect cardiac, hepatic, renal, neural or hematopoietic systems. It may favorably influence the electrical activity of the brain, blood pressure, and sleep. (A recent study (14) has shown that Metrazol is excreted in its original form, mainly through the kidney, and reaches peak excretion in about four hours.)

As a postscript to the present study it may be well to point out that the subtle action of Metrazol when given orally contrasts strikingly with the effects of the subconvulsive intravenous administration of this drug (15). Although the effects

are apparently more spectacular with the latter method, the hazard is far greater and many additional difficulties are encountered.

SUMMARY

A group of researchers from eight disciplines have studied the effects of oral pentylenetetrazol (Metrazol) on the psychoses of the senium, using a relatively pure sampling of 30 institutionalized women whose average age was 76.6 years. The patients were divided into experimental and control groups, the former receiving Metrazol plus vitamins, the latter vitamins alone. The observed criteria consisted of physiologic, psychologic, and psychiatric areas. Data were accumulated according to rating scales. Metrazol was administered in doses of 0.2 Gm. four to six times daily over a period of seventeen months. The identities of the patients were known only to the project director. The results of the first nine months of research are reported—June 1952 to March 1953.

The data and observations were analyzed statistically and clinically. No significance of change was noted statistically, but a definite trend toward improvement was found in the Metrazol-treated group. Improvement was striking on the basis of clinical estimates and took place in the feeling of well-being, alertness, clarity of thought, orientation, and personal relationships.

It was further found that the beneficial effects of the drug develop subtly. Hence it is recommended that the drug not be abandoned unless results are negative after six to eight weeks of administration.

Metrazol was found to be physiologically harmless.

The recommendation is made that the use of this drug always be supplemented by a psychotherapeutically fertile program.

The values of interdisciplinary research and some of the significant psychiatric and physiologic details are discussed. The form for recording the observed indices used for grading the patients is reproduced and results are presented in tabular form.

Acknowledgments

The authors wish to express their gratitude and indebtedness to the following, without whose help this project would not have been possible:

Mrs. Edna B. Shaw, R.N., in charge of nurse observers;

Salvatore Carfagno, M.D., Internist;

Stanley H. Cath, M.D. and Stanley M. Kemler, M.D., in charge of interpretation of EEG's;

John Wooten, Electro-Diagnostic technician;

M. Harold Book, M.D. and his Pathology Laboratory Staff; and

The entire staff and personnel of the Institute for Research in Human Relations, Philadelphia, Pa.

REFERENCES

1. Linden, M. E., and Courtney, D.: The human life cycle and its interruptions: a psychologic hypothesis. Studies in gerontologic human relations. I., *Am. J. Psychiat.* **109:** 906–915, 1953.
2. Linden, M. E.: Significance of dual leadership in gerontologic group psychotherapy. Studies in gerontologic human relations. III., *Internat. J. Group Psychotherap.* **4:** 262–273, 1954.

3. Freyhan, F. A.; Woodward, R. B., and Kety, S. S.: Cerebral blood flow and metabolism in psychoses of senility, *J. Nerv. & Ment. Dis.* **113:** 449–456, 1951.
4. Doust, J. W. L.; Schneider, R. A.; Talland, G. A.; Walsh, M. A., and Barker, G. B.: Studies on the physiology of awareness. The correlation between intelligence and anoxemia in senile dementia, *J. Nerv. & Ment. Dis.* **117:** 383–398, 1953.
5. Levy, S.: Pharmacological treatment of aged patients in a State mental hospital, *J.A.M.A.* **153:** 1260–1265, 1953.
6. Clow, H. E.: Individualizing the care of the aging, *Am. J. Psychiat.* **110:** 460–464, 1953.
7. Linden, M. E.: Group psychotherapy with institutionalized senile women. Studies in gerontologic human relations. II., *Internat. J. Group Psychotherap.* **3:** 150–170, 1953.
8. Hollender, M. H.: Role of the psychiatrist in homes for the aged, *Geriatrics* **6:** 243–250, 1951.
9. Meerloo, J. A. M.: Contribution of psychoanalysis to problems of the aged *in* Psychoanalysis and Social Work, ed. by M. Heiman. New York, Interscience Publishers, Inc., 1953, p. 321.
10. Goldfarb, A. I.: Recommendations for psychiatric care in a home for the aged, *J. Gerontol.* **8:** 343–347, 1953.
11. Chesrow, E. J.; Giacobe, A. J., and Wosika, P. H.: Metrazol in arteriosclerosis associated with senility, *Geriatrics* **6:** 319–323, 1951.
12. Linden, M. E.: Transference in gerontologic group psychotherapy. Studies in gerontalogic human relations. IV., *Internat. J. Group Psychotherap.* **5:** 61–79, 1955.
13. Andosca, J. B.: Effects of pentylenetetrazol on senile patients. A clinical study, *New England J. Med.* **250:** 461–463, 1954.
14. Esplin, D. W.; Woodbury, D. M., and Goodman, L. S.: Distribution, fate and excretion of pentylenetetrazol, *Fed. Proc.* **13:** 352, 1954.
15. Lieberman, A. L. Subconvulsive intravenous Metrazol therapy in mental patients. A preliminary report, *Geriatrics* **9:** 125–127, 1954.

TUBE FEEDING WTIH NATURAL FOODS IN ELDERLY PATIENTS

JAMES BARRON, M.D. AND LAURENCE S. FALLIS, M.D.

The Department of Surgery, Henry Ford Hospital, Detroit, Michigan

The nutritional status of the patient is one of the most important factors in determining a favorable outcome of any medical or surgical program of treatment. It has long been recognized that the vital reserves of geriatric patients are limited and, as a consequence, the risk of operation is greater. The value of restoring nutritional balance in this group of patients is only now receiving the emphasis it deserves.

The question of how best to correct these substandard nutritional states has received considerable attention. There are two routes for the administration of supplementary feeding—oral and intravenous. In recent years emphasis has been directed toward the latter. However, most will agree that the oral route, if it can be used, is superior. In natural whole foods such as milk, eggs, meat, vegetables and fruit there is an excellent natural source of proteins, fats, carbohydrates, vitamins, minerals and other as yet unidentified essential nutrients. Moreover, the gastro-intestinal tract is already long accustomed to handling these foods and excellent tolerance can be readily predicted.

Elderly patients of the type shown in Figures 1, 2 and 3, often with little or no desire to live, present some of the most difficult feeding problems. These aged arteriosclerotic cerebro-degenerative individuals, weakened by malnutrition and often made more irritable by the presence of decubitus ulcers, respond poorly to the suggestion that they should increase their oral intake of food. Inability to masticate due to loss of teeth and poor oral hygiene contributes to an almost impossible situation so far as the oral ingestion of food is concerned.

Tubing

It is in conditions such as this that tube feeding provides the answer. There are now available small non-irritating plastic tubes (1) which can be readily passed into the upper gastro-intestinal tract and kept in place for long periods of time. Techniques have been devised for passing tubes in those who cannot or will not cooperate in swallowing. These polythene tubes have an outside diameter of 2.5 mm. or less and, being impermeable, do not convey taste of the food; this factor alone is of tremendous help in elderly patients. A small-calibre tube will pass through areas of partial obstruction and may be used in any case in which there is no obstruction of the lower gastro-intestinal tract.

Liquefied food mixture

At the Henry Ford Hospital we have now been using natural foods for tube feeding since 1951 (2) and from the standpoint of cost, tolerance and clinical response they have surpassed any formula-prepared materials that we have tried. Natural foods are good sources of protein and calories, at low cost. For example, one quart of homogenized milk at a cost of 22 cents contains 35 Gm. of

FIG. 1. Patient aged 86. Resection of rectosigmoid. Refused to eat. Decubitus ulcers marked weight loss; soreness of tongue and gums; edema; and anemia. Tube feeding started, 4000 to 5000 calories daily. All evidence of malnutrition disappeared and excellent appetite returned.

With this apparatus position makes no difference in the pump delivery rate. The patient may sit up or lie down as desired. The food is kept in a pan of cracked ice.

protein and provides 700 calories. One egg contains 6 Gm. of protein (75 calories); and two ounces of medium fat beef or ham contains 14 Gm. of protein (145 calories).

Milk and strained fruit juices will pass through the small tubes without difficulty. These solutions can be liberally used in the liquefaction of meat, eggs, fruit and vegetables. For small amounts, mechanical blenders (such as the Waring or Oster types) are satisfactory. Bones and seeds must be removed and the machine should be allowed to run long enough to homogenize the food thoroughly. The mixture must be strained through a fine-mesh wire gauze strainer in order to prevent plugging of the small tube. The demand for this product in our own institution has been so great that we have had to make it in large quantities. Serum (colloid) mills (3) of 5-gallon and 20-gallon capacity are are excellent for large-scale preparation of liquefied food for this purpose. The diet can be varied a great deal; indeed, better tolerance results if a reasonable attempt is made to keep the composition of the tube-feeding mixture about the same as the usual diet to which the patient is accustomed. If a blender or serum mill is not readily available, strained meats and vegetables (*e.g.*, Gerber or Heinz baby foods) which are obtainable in almost any grocery store can be used, and have the advantage of not needing to be strained. At a total retail cost of 60 cents

TUBE FEEDING WTIH NATURAL FOODS IN ELDERLY PATIENTS

JAMES BARRON, M.D. AND LAURENCE S. FALLIS, M.D.

The Department of Surgery, Henry Ford Hospital, Detroit, Michigan

The nutritional status of the patient is one of the most important factors in determining a favorable outcome of any medical or surgical program of treatment. It has long been recognized that the vital reserves of geriatric patients are limited and, as a consequence, the risk of operation is greater. The value of restoring nutritional balance in this group of patients is only now receiving the emphasis it deserves.

The question of how best to correct these substandard nutritional states has received considerable attention. There are two routes for the administration of supplementary feeding—oral and intravenous. In recent years emphasis has been directed toward the latter. However, most will agree that the oral route, if it can be used, is superior. In natural whole foods such as milk, eggs, meat, vegetables and fruit there is an excellent natural source of proteins, fats, carbohydrates, vitamins, minerals and other as yet unidentified essential nutrients. Moreover, the gastro-intestinal tract is already long accustomed to handling these foods and excellent tolerance can be readily predicted.

Elderly patients of the type shown in Figures 1, 2 and 3, often with little or no desire to live, present some of the most difficult feeding problems. These aged arteriosclerotic cerebro-degenerative individuals, weakened by malnutrition and often made more irritable by the presence of decubitus ulcers, respond poorly to the suggestion that they should increase their oral intake of food. Inability to masticate due to loss of teeth and poor oral hygiene contributes to an almost impossible situation so far as the oral ingestion of food is concerned.

Tubing

It is in conditions such as this that tube feeding provides the answer. There are now available small non-irritating plastic tubes (1) which can be readily passed into the upper gastro-intestinal tract and kept in place for long periods of time. Techniques have been devised for passing tubes in those who cannot or will not cooperate in swallowing. These polythene tubes have an outside diameter of 2.5 mm. or less and, being impermeable, do not convey taste of the food; this factor alone is of tremendous help in elderly patients. A small-calibre tube will pass through areas of partial obstruction and may be used in any case in which there is no obstruction of the lower gastro-intestinal tract.

Liquefied food mixture

At the Henry Ford Hospital we have now been using natural foods for tube feeding since 1951 (2) and from the standpoint of cost, tolerance and clinical response they have surpassed any formula-prepared materials that we have tried. Natural foods are good sources of protein and calories, at low cost. For example, one quart of homogenized milk at a cost of 22 cents contains 35 Gm. of

FIG. 1. Patient aged 86. Resection of rectosigmoid. Refused to eat. Decubitus ulcers marked weight loss; soreness of tongue and gums; edema; and anemia. Tube feeding started, 4000 to 5000 calories daily. All evidence of malnutrition disappeared and excellent appetite returned.

With this apparatus position makes no difference in the pump delivery rate. The patient may sit up or lie down as desired. The food is kept in a pan of cracked ice.

protein and provides 700 calories. One egg contains 6 Gm. of protein (75 calories); and two ounces of medium fat beef or ham contains 14 Gm. of protein (145 calories).

Milk and strained fruit juices will pass through the small tubes without difficulty. These solutions can be liberally used in the liquefaction of meat, eggs, fruit and vegetables. For small amounts, mechanical blenders (such as the Waring or Oster types) are satisfactory. Bones and seeds must be removed and the machine should be allowed to run long enough to homogenize the food thoroughly. The mixture must be strained through a fine-mesh wire gauze strainer in order to prevent plugging of the small tube. The demand for this product in our own institution has been so great that we have had to make it in large quantities. Serum (colloid) mills (3) of 5-gallon and 20-gallon capacity are are excellent for large-scale preparation of liquefied food for this purpose. The diet can be varied a great deal; indeed, better tolerance results if a reasonable attempt is made to keep the composition of the tube-feeding mixture about the same as the usual diet to which the patient is accustomed. If a blender or serum mill is not readily available, strained meats and vegetables (*e.g.*, Gerber or Heinz baby foods) which are obtainable in almost any grocery store can be used, and have the advantage of not needing to be strained. At a total retail cost of 60 cents

FIG. 2. Patient aged 76. Biliary fistula; anemia and decubitus ulcer. Refused to eat. All bile was collected and pumped with food into the stomach. Biliary fistula completely healed and appetite excellent after three weeks of feeding program.

there can be included one 3½-ounce jar of meat, one 4½-ounce jar of vegetables, 3 eggs, and ⅔ quart of homogenized milk. This mixture will provide 60 Gm. of protein (840 calories).

Factors in administration

Early in our work with tube feeding we became convinced that a mechanical food pump was almost a necessity (4). The advantages over the gravity-drip method are many. The feeding mixture can be thicker and the patient can change position at will. This is an important consideration, whether the patient be bed-ridden or ambulatory. In all seriously ill, and especially in elderly patients, a slow constant delivery is most essential in order to prevent vomiting or diarrhea. It is always preferable to take as long as eight to ten hours to deliver 1 liter of the food, which contains from 40 to 75 Gm. of protein. Constipation and fecal impaction must be continually watched for, especially in the aged. The rate of food intake can be rapidly increased as the patient's gastro-intestinal function improves. Vitamins and minerals are usually not added to the whole food.

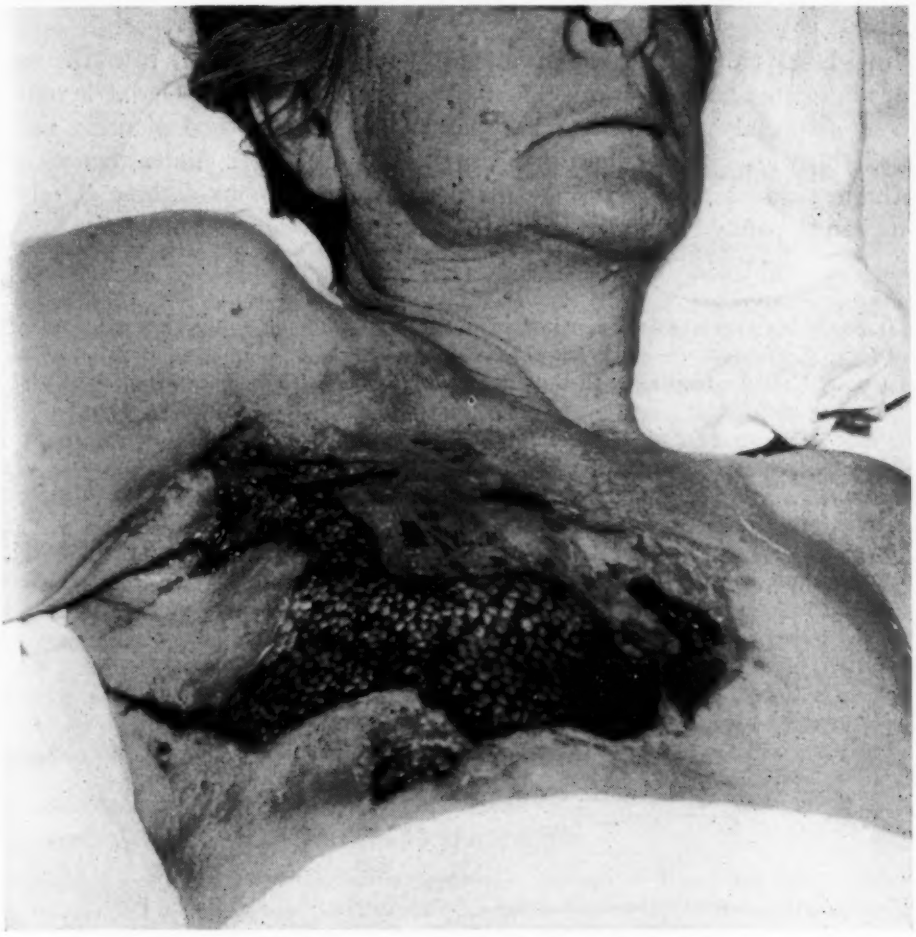

FIG. 3. Patient aged 74. Mastectomy. Refused to eat and had no desire to live. Granulation tissue gray, with poor vascularity. Fed with 4000 to 6000 calories through tube daily. Granulation tissue soon became healthy. Pinch grafts were 100 per cent successful. After three and a half weeks of feeding, patient began to eat well voluntarily.

Types of patients

We have used this liquefied food in increasing amounts for well over four years. Typical of the geriatric patients in whom this type of feeding has been employed are those with carcinoma of the tongue, lip, pharynx, esophagus and stomach, anorexia, decubitus ulcers, cerebrovascular accidents, fistulae of the upper gastro-intestinal tract, malnutrition, coma, fractures, delayed emptying after gastrectomy, diarrhea, or dysphagia (5). Restoration of the nutritional balance by this method of forced tube feeding has salvaged many elderly patients who previously would have been lost. The ingestion of liquefied natural food stimulates a return of appetite and induces in the patient a real desire to get well, with the result that the signs and symptoms of malnutrition disappear.

SUMMARY

Nutritional balance can be restored by natural foods put into the upper gastro-intestinal tract by means of small non-irritating tubes. Geriatric patients present a special opportunity for application of this method of using natural foods, which are cheaper, better tolerated, and of greater clinical benefit than synthetic products. By restoring nutritional balance, more of these elderly patients can be safely brought through their medical or surgical programs.

REFERENCES

1. Fallis, L. S., and Barron, J.: Gastric and jejunal alimentation with fine polyethylene tubes, *A. M. A. Arch. Surg.* **65:** 373–380 (Sept.) 1952.
2. Barron, J.: Tube feeding with liquefied natural foods, *Henry Ford Hosp. Med. Bull.* **1:** 13–17 (June) 1953.
3. Barron, J., and Fallis, L. S.: Tube feeding with liquefied whole food, *Surg. Forum, Am. Coll. Surg.* 1953, pp. 519–522.
4. Barron, J., and Prendergast, J. J.: Food pumps—a new approach to tube feeding (to be published).
5. Howell, J. T., and Monto, R. W.: Syndrome of anemia, dysphagia and glossitis (Plummer-Vinson syndrome), *New England J. Med.* **249:** 1009–1012 (Dec. 17) 1953.

Abstracts of Current Literature

TREATMENT OF CARDIOVASCULAR DISEASE WITH ANTICOAGULANTS.
Adams, W. R. *Postgrad. Med.* **17:** 1 (Jan.) 1955.

Indications for the use of anticoagulant therapy are: 1) coronary thrombosis with myocardial infarction, 2) exacerbation of coronary insufficiency, 3) rheumatic heart disease with auricular fibrillation and emboli, 4) venous thrombosis (thrombophlebitis, phlebothrombosis, migrating thrombophlebitis), 5) arterial embolism or thrombosis, 6) pulmonary embolism, and 7) after operation, to prevent thrombo-embolism. The first of these is an important indication. The desirability is suggested of using anticoagulants in every case of myocardial infarction, provided good laboratory control is available. Contraindications to anticoagulant therapy are: 1) lack of a reliable prothrombin-time laboratory, 2) an erratic or uncooperative patient, 3) prothrombin deficiency, 4) renal insufficiency, 5) ulcers, surgery or trauma, 6) hemorrhagic disease, and 7) subacute bacterial endocarditis. All of these are relative contraindications inasmuch as the use of anticoagulants may be desirable in some desperate situations despite the increased risk of hemorrhage. A prothrombin index is used in controlling dosage. Its use is imperative because there is no such thing as an average dosage. Several cases illustrate how the situation may get out of control if the dosage of anticoagulant is not carefully adjusted as indicated by frequent determinations of the prothrombin time. Dicumarol is a potent, useful adjunct in the treatment of thrombo-embolic disease. It may be used in intelligent, cooperative patients. The fields of its usefulness are well defined except that further investigation is necessary to establish its role in mild diseases and in the prevention of emboli.

THE PROBLEM OF GALLSTONES IN THE AGED.
Andresen, A. F. R. *M. Times* **83:** 46 (Jan.) 1955.

Gallstones are found most often in persons over the age of 40 and are most common in women. Careful management and individual selection of patients for operation can accomplish much in reducing the necessity for, and the mortality from, surgical treatment for gallstones in aged persons. The diagnosis, the surgical and medical treatments of gallstones, and the treatment of biliary colic are discussed. A complete study of the patient should always accompany the diagnosis of gallstones. Associated diseases and focal infections must be treated. Consideration of the anatomy and physiology of the biliary tract provides the basis for recommended treatment in patients with gallstones. Frequent feedings and a well balanced diet containing adequate fat and vitamins promote normal biliary function and are highly important in maintaining the health of the elderly patient. The inadequate diets often prescribed are a frequent cause of distress in themselves. When the elderly patient becomes free of symptoms, operation may be unnecessary, even if the presence of stones has been demonstrated. After an operation for gallstones, the gallbladder diet and frequent feedings are necessary in order to promote biliary drainage.

ACTH AND CORTISONE IN THE TREATMENT OF ASTHMA.
Baldwin, H. S.; DeGara, P. F.; Spielman, A. D., and Dworetzky, M. *J. Allergy* **26:** 44 (Jan.) 1955.

Sixty patients with severe status asthmaticus were treated with ACTH and cortisone, alone or in combination. The usefulness of these hormones in the treatment of asthma, the complications attributable to their use, the proper dosage, alternation of ACTH and cortisone therapy, and the relation of hormone therapy to adrenal function, respiratory

function and other medical management were investigated. Twenty-five of the patients were over 40 years of age. Fourteen patients received total doses of cortisone exceeding 10 Gm.; the largest total dose was 62 Gm. The longest period of observation for cortisone administration was thirty-nine months. The total doses of HP Acthar gel exceeded 2,000 units in 11 patients. The largest total dose was 7,780 units, and the longest period of observation was thirty-four months. Satisfactory results were obtained in 52 of the patients. Continued hormone therapy was necessary to maintain symptomatic relief in 30 patients. Alternating or combined administration of HP Acthar gel parenterally and cortisone orally was effective in patients requiring long-term therapy. Complications developed infrequently; they necessitated discontinuation of treatment in only 3 patients. It was found advisable to use the minimum dosage of the hormone that would keep the patient comfortable during maintenance therapy. Therapy with ACTH and cortisone is safe and effective in patients with asthma if they are carefully selected, kept under observation, and given over-all management.

THE GALLBLADDER AND THE HEART.

Becker, M. C.; Bernstein, A., and Kaufman, J. G. *J. Newark Beth Israel Hosp.* **6:** 84 (Jan.) 1955.

The relation between the gallbladder and arteriosclerotic heart disease is discussed with reference to various statistical studies and experimental work reported in the literature. Disease of the gallbladder is often associated with coronary arteriosclerosis, but is not an etiologic agent in coronary artery disease. Their frequent coexistence is probably the result of a common denominator. Apparently, gallbladder disease causes or aggravates cardiac symptoms only when coronary artery disease is already present. The distribution of the pain often enables the physician to distinguish between pain from gallbladder disease and pain of cardiac origin. However, atypical cases exist. Referred pain can cause considerable difficulty in diagnosis, as is shown by the case report of a woman in whom the symptoms of a rupturing gallbladder simulated those of myocardial infarction. Another case report illustrates the rare condition in which coronary occlusion simulates gallbladder disease. The authors have found that routine electrocardiographic examination of all patients considered for gallbladder surgery results in a decrease in the incidence of surgery on patients with myocardial infarction and aids in the detection of coexisting coronary and acute gallbladder disease. Electrocardiograms are also made postoperatively. Cholecystography and other gastrointestinal studies are carried out on patients with suspected coronary artery disease who have atypical angina or equivocal electrocardiograms and minor T-wave changes.

COMBINED TRIGEMINAL AND GLOSSOPHARYNGEAL NEURALGIA.

Brzustowicz, R. J. *Neurology* **5:** 1 (Jan.) 1955.

Trigeminal neuralgia and glossopharyngeal neuralgia, the major types of neuralgia that cause paroxysmal attacks of pain in the face, occur most frequently in persons over 40 years of age. Trigeminal neuralgia occurs about 75 times as often as does glossopharyngeal neuralgia, affects women more frequently than men, and involves the right side more often than the left. Rarely, it may occur bilaterally. In glossopharyngeal neuralgia, the incidence is about the same in both sexes and on both sides. Combined trigeminal and glossopharyngeal neuralgia occurred in 9 of a series of 34 patients observed at the Mayo Clinic between 1935 and 1950. All 9 patients were over 40 years of age. The combined neuralgia affected the left side in 7 and the right side in 2. Trigeminal neuralgia appeared first in 7 of the patients. Case reports of the 9 patients illustrate the problems encountered in differential diagnosis. Glossopharyngeal neuralgia may be confused with neuralgia of the third division of the trigeminal nerve. The distribution of the pain, rather than its character or duration, is helpful in distinguishing between the two types. In glossopharyngeal neu-

ralgia, the pain extends from the region of the tonsillar fossa and pharynx deep in the neck to the ear. It is not brought on by touching or rubbing the face, but can be induced by swallowing or yawning. Cocainization of the tonsillar fossa results in temporary relief. If the pain is due to neuralgia of the third division of the trigeminal nerve, cocainization of the tonsillar fossa brings no relief. Injection of alcohol into the third division of the trigeminal nerve does not affect pain due to glossopharyngeal neuralgia. Consideration of the anatomic distribution of pain fibers in the trigeminal, facial, glossopharyngeal and vagus nerves, and of the occurrence of the neuralgia in patients past 40 years of age, indicates that trigeminal neuralgia may be caused by ischemia in the trigeminal tracts or nuclei. A similar mechanism probably accounts for neuralgia in the facial, glossopharyngeal or vagus nerves. In glossopharyngeal neuralgia, unless the pain is relieved by medication, section of the glossopharyngeal nerve using a suboccipital approach is indicated. In trigeminal neuralgia, injection of alcohol into the branches of the trigeminal nerve, or other medication, may bring relief. The surgical treatment of trigeminal neuralgia includes partial or complete section of the sensory root of the trigeminal nerve, through either a temporal or a suboccipital approach, and the trigeminal tractotomy of Sjöqvist. The latter procedure is particularly applicable when both glossopharyngeal and trigeminal neuralgia are present. Seven of the patients with combined neuralgia received surgical treatment.

EVALUATION OF PROLONGED CORTISONE THERAPY IN RHEUMATOID ARTHRITIS. A FOUR-YEAR STUDY.

Bunim, J. J.; Ziff, M., and McEwen, C. *Am. J. Med.* **18:** 27 (Jan.) 1955.

Data are presented from the observation of 71 patients with rheumatoid arthritis who received cortisone for periods varying from a few weeks to four years. Among the 64 patients who could be followed, the maintenance dosages were 25 to 50 mg. in 18; 60 to 100 mg. in 43; and more than 100 mg. in 3 patients. At forty-two months, 11 patients were under observation and 9 were still receiving cortisone. The results are analyzed according to duration and stage of the arthritis, duration of therapy, functional improvement, comparison of factors in groups with excellent and poor responses, occurrence of undesirable effects, and appearance or extension of bone destruction despite a good clinical response. Adrenocortical steroids, such as cortisone, are concluded to be useful agents in properly selected cases of rheumatoid arthritis. Patients in whom the disease is severe, reversible, of recent development, and rapidly progressive appear best suited for steroid therapy. Also those are suitable who require only moderate dosages for control of their arthritis, present no contraindications, and are not unusually susceptible to the side effects of the steroid. Many patients can tolerate maintenance dosages of cortisone for several years without becoming refractory and without clinical evidence of adrenocortical insufficiency. Assets of steroid therapy are a high rate of therapeutic response, especially in the early months of treatment, early recovery of good functional capacity with restoration of employability and self-sufficiency, and aid in rehabilitation. The undesirable side effects are largely reversible and many disappear during continued steroid administration. Limitations of steroid therapy include failure to alter or arrest the extension of the pathologic processes of the disease, the frequent occurrence of relapses when the drug is discontinued, and the occasional development of serious complications or side effects with prolonged administration. In this series, peptic ulcer occurred in 5 patients (with perforation in 2), fractures in 4, and death from overwhelming sepsis in 1 patient.

LIVER FUNCTION STUDIES AFTER PROLONGED COUMARIN THERAPY.

Elster, B. B., and Eisenstadt, H. B. *Texas J. Med.* **51:** 18 (Jan.) 1955.

Thirty-five patients were treated for from six to sixty months with Dicumarol or Cumopyran. They were kept at prothrombin levels of 20 to 40 per cent. There were 14 abnormal liver function results: 5 bromsulphalein retentions, 1 positive Hanger flocculation, 2 increased serum alkaline phosphatase values, 3 low serum albumin levels, and 3 high serum

globulin levels. Among the 11 patients with deviations from normal, 3 showed multiple abnormalities and 8 single alterations. The severe cardiovascular diseases with extracardiac complications in the former group might have accounted for the altered results in the hepatic function tests. In the remainder, a single abnormal liver function test result was considered insufficient evidence of hepatic disease. Despite continued use of anticoagulants, none of the abnormal findings showed progression upon periodic re-check. Clinically, there was no evidence of hepatic damage. The coumarin derivatives appear to be the drugs of choice for prolonged anticoagulant therapy.

DEAFNESS IN OLDER PERSONS.

Fabricant, N. D. *Eye, Ear, Nose & Throat Monthly* **34:** 54 (Jan.) 1955.

In the past few years, the increasing awareness of the seriousness of hearing loss to the patient has resulted in an emphasis on aural rehabilitation. Adjustment to the disability is particularly important in older patients, for treatment will only rarely result in a cure or significant improvement in those with total or nearly total hearing impairment. Emphasis on adjustment rather than on possible improvement in hearing is advisable, even when the otologic findings are favorable. The most frequent cause of deafness in older persons is presbycusis. This results from arteriosclerotic and degenerative changes and involves a loss of hearing for high pitched tones, which increases with advancing age. The average hearing loss in older patients is 40 decibels. In addition to the loss of hearing for high pitched tones, audiometric examination reveals lowering of the upper tone limit and a shortening of the bone conduction time. Tinnitus and the recruitment phenomenon are also found. The disease progresses very slowly. Hearing tests often fail to account for the subjective degree of deafness. In older patients, lack of attention may serve to exaggerate the hearing loss and cause poor discrimination of sounds. Arteriosclerotic deafness is also found chiefly in older persons. The hearing loss applies to all frequencies. The involvement is usually unilateral or is more pronounced unilaterally. Tinnitus frequently occurs in the more severely affected ear.

A CYTOLOGIC EVALUATION OF THE PROSTATIC SMEAR IN CARCINOMA OF THE PROSTATE.

Frank, I. N. *J. Urol.* **73:** 128 (Jan.) 1955.

The microscopic examination of material expressed from the prostate by digital massage is of value in determining the presence of a carcinoma in that gland. The secretions obtained in this manner are fixed, stained and examined by a standardized procedure. Cytologic criteria of malignancy, a fixed classification system, and characteristic cell types are discussed. A three-year survey of prostatic smears from 1,052 patients revealed that a positive cytologic report was correlated with at least an 85 per cent accuracy. A breakdown of the suspicious and positive classifications is tabulated with further information regarding case findings, false positives, and false negatives. Close co-operation between the clinician and the cytologist is stressed. It is concluded that the prostatic smear offers a reliable adjunct to the diagnosis of prostatic carcinoma, a means of detecting an occasional case which is clinically unsuspected, and a technique suitable for assaying estrogen response. (Author's summary.)

THE AGE FACTOR IN THE MORTALITY RATE OF PATIENTS UNDERGOING SURGERY OF THE BILIARY TRACT.

Glenn, F., and Hays, D. M. *Surg., Gynec. & Obst.* **100:** 11 (Jan.) 1955.

The age factor in the surgical treatment of biliary-tract disease is analyzed by using an experience with a series of 4,050 patients treated surgically in this medical center. Among patients under 50 years of age, the rate of fatal complications in nonmalignant disease of the biliary tract was 0.65 per cent. Among patients 50 to 64 years old this rate was 2.5 per cent; and among patients over 65 years of age it increased to 6.7 per cent. For elective

surgical procedures the difference in mortality is not significant. The high mortality rate among aged patients occurs following emergency surgery. Thus the complications of acute cholecystitis in the aged patient with degenerative disease are the chief factor in the operative risk. Operation should be performed in older patients with acute cholecystitis but they merit the most meticulous care in surgical management. This includes operation as early as possible in an acute attack before complications such as perforation, stone obstruction, and jaundice appear. The authors' experience appears to justify the policy of regarding all calculus cholecystitis, whether symptomatic or not, as a potential hazard and an indication for elective cholecystectomy. Unique aspects of biliary-tract disease in the aged include: (a) an increased incidence of acute cholecystitis; (b) an increased incidence of choledocholithiasis, with larger and more numerous choledochal calculi; (c) the occurrence of acute processes in the biliary tract with minimal signs and symptoms; and (d) the increased incidence of associated biliary-tract neoplasia. (From authors' summary.)

MYOCARDIAL INSUFFICIENCY DURING OPERATION. ITS RECOGNITION AND TREATMENT WITH ACETYL STROPHANTHIDIN.

Greene, B. A. and Berkowitz, S. *New York State J. Med.* **55:** 57 (Jan.) 1955.

The use of acetyl strophanthidin in the diagnosis and treatment of acute myocardial insufficiency during surgery in 29 patients is discussed. The rapid and brief digitalizing action of the drug and the adequate margin of safety make it a valuable agent when carefully used. Twenty-two of the 29 patients were over 60 years of age. In some of the patients, congestive failure was obvious, but in patients suffering from shock, the detection of myocardial insufficiency was difficult. Digitalization was used in shock only when the criteria for such treatment were clearly present and other measures failed to bring relief. Among several hundred cases of shock, digitalization appeared to be indicated in only 18. The chief indications for treatment with acetyl strophanthidin in the 29 patients were pulmonary edema, rapid ventricular rate with auricular fibrillation, and shock. Twenty of the group were known to have heart disease before operation. Eight of these had been digitalized during the week preceding operation. Treatment with acetyl strophanthidin was beneficial, and the operation was successfully completed, in every instance. The authors recommend, in patients who have not been digitalized in the preceding ten days, an initial intravenous injection of 0.6 mg. of acetyl strophanthidin followed by doses of 0.2 mg. every ten or fifteen minutes until the desired therapeutic effect, or toxic effects, appear. In a patient who has received digitalis within the preceding ten days, the initial and subsequent doses should be 0.2 mg. Nine case reports are presented.

REHABILITATION IN THE OLDER AGE GROUP.

Greene, L. B., and Sokolow, J. *Postgrad. Med.* **17:** 43 (Jan.) 1955.

If the attitude persists that the aged must be placed in nursing homes if care at home becomes too much of a problem, our aged population will become the permanent inhabitants of nursing homes and hospitals. The concept of treating the total individual with a view toward his living a full life to the limits of his abilities, has broadened the horizon for the aged. What can be done in rehabilitation to prevent commitment to a nursing home is illustrated by the case of a 69-year-old man who had a cerebrovascular accident with right hemiplegia and slurring of speech. He recovered sufficiently to return to work. Following a virus infection a few months later, deterioration in coordination and ability to walk commenced. After two years, he could stand but could not walk. He was severely depressed. His speech was slurred and almost inaudible. Muscle tests showed moderate generalized weakness of the trunk and lower extremities. Abnormal neurologic findings were a positive Romberg sign and right facial paresis. A program of coordination exercises, ambulation training, and occupational and speech therapy was started. Treatment was given twice weekly for half a day and coordinated with exercises at home. The patient was given 50 mg. of Benadryl four times daily. He rapidly improved physically and emotionally, became able to walk without hesitation, and had more endurance. He talked voluntarily and in a

clearer voice. Home maintenance was possible for this patient without his being a burden to his family.

PROSTATIC CANCER. VI. MORTALITY RATE OF RADICAL SURGERY FOR ADENOCARCINOMA OF THE PROSTATE.

Hudson, P. B.; Finkle, A. L., and Hopkins, J. A. *J. Urol.* **73:** 139 (Jan.) 1955.

Surgical procedures for the treatment of various types of cancer are reviewed in terms of their efficacy and the mortality rates. Prostatic cancer, an important cause of death among older men, is a type of malignancy for which radical surgical treatment is feasible. Postoperative mortality rates and cure rates for total prostatectomy are cited. The authors add to the record a series of 52 radical prostatectomies performed at the Francis Delafield Hospital between March 1951 and July 1953, in which the mortality rate was 1.9 per cent. They believe that the low mortality rates and comparatively high cure rates justify increased use of total prostatovesiculectomy in the treatment of prostatic cancer.

SENILE TONSILLAR GIGANTISM. REPORT OF A CASE.

King, J. T. *South. M. J.* **47:** 1155 (Dec.) 1954.

A case of tonsillar gigantism in a 68-year-old man is reported. Only 2 cases of massive hypertrophy of the tonsils in persons over 60 years of age were found reported in the English and American literature of the past fifty years. In the present case, the size of the tonsils caused difficulty in breathing and swallowing. When first seen, in November 1949, the patient had experienced this difficulty for a year. Two years later the patient could swallow only liquids, could breathe only when sitting up, and was so weak that he was unable to walk. The tonsillar masses almost completely filled the pharynx. No acute inflammation was apparent. A tonsillectomy was performed in January 1952. The ability to breathe and swallow returned to normal. The pathologic finding was severe chronic and active tonsillitis. There was no evidence of tumor or of Brill-Symmers disease. The combined weight of the tonsillar masses removed was 20 Gm.

AUTOINTOXICATIONS AND PROCESSES OF AGEING.

Korenchevsky, V. *Texas Rep. Biol. & Med.* **12:** 1006 (Winter) 1954.

Data are collected and reviewed which suggest that autointoxications by metabolic products and products of intestinal putrefaction may be among the causes of premature aging and death. Experiments on animals and observations on man agree that over-feeding increases the level of metabolites in the blood and tissues, thus increasing the incidence and early appearance of degenerative diseases of old age and causing premature death. Although the results with high protein diets have been contradictory, harmful effects have usually been recorded when the diet was given for a long time, neutralizing mechanisms were made deficient, older animals were used, and the type of proteins ingested was considered. Some amino acids, purines and their derivatives, and some other metabolites proved toxic in varying degrees when administered at levels beyond physiologic limits. Some intestinal putrefaction products also proved toxic. Toxic metabolites cause pathologic changes, particularly in the liver, kidneys and cardiovascular system. The changes include various forms of nephrosis, nephritis, myocarditis, lesions of the blood vessels, cirrhosis of the liver, gastric ulcer, parathyroidectomy-like features, gliosis of the brain, and tumors. As with other compounds, small doses of certain metabolites have physiologic effects, whereas larger doses may have abnormal or toxic effects. In elderly men, the level of one of five metabolites studied (creatine) was increased over that in young men. Frequent changes in the nutritional medium of isolated tissue cultures prevented their aging, probably because cellular waste products were removed; cells from old animals were made similar to those from younger ones by this procedure. "Blood-washing" solutions—intravenous physiologic saline, slightly hypertonic Ringer's solution, sodium citrate solution—used in the treatment of elderly persons with thrombo-angiitis obliterans and arteriosclerosis of

the peripheral vessels usually benefited or cured local lesions and the patients' general condition improved. These effects appear to have resulted from the removal of excessive quantities of metabolites that had accumulated in the blood and tissues. The intestinal bacterial flora of milk-fed children consists largely of lactic bacteria. With aging, putrefactive bacteria and other microbes invade the intestine. They have been replaced with lactic microbes by administering milk fermented by these bacteria. The data cited were inadequately investigated but all suggest the same conclusion. (170 references.)

DIZZINESS OF OBSCURE ETIOLOGY.

Kos, C. M. *J. Iowa M. Soc.* **45:** 13 (Jan.) 1955.

The clinical disorder called Ménière's symptom complex involves vertigo, tinnitus, hearing loss, nystagmus, and associated autonomic phenomena in patients in whom dizziness cannot be ascribed to the degenerative changes of old age and in whom the cause of the dizziness is not apparent on otologic or neurologic examination. Further classification of the clinical patterns observed is possible when the function of hearing and the patient's history are taken into account. Depending on the duration of the resulting changes and the extent to which they affect the labyrinth, so-called idiopathic dizziness can be classified into labyrinthine hydrops (Ménière's disease), labyrinthine ischemia, and labyrinthine apoplexy. The characteristics, diagnosis, prognosis, and treatment of each of these conditions are discussed. Labyrinthine hydrops occurs most frequently in persons between 35 and 45 years of age. The dizziness is spontaneous and paroxysmal. Labyrinthine ischemia is due to degenerative changes and occurs most often in persons over 45 years of age. It is frequently associated with arteriosclerosis. The dizziness accompanies movement and certain positional attitudes, and it is likely to be more severe at certain times of the day. In labyrinthine apoplexy, an acute destructive process, a true vertigo persists for three to four weeks or more. The hearing impairment is likely to remain. The degree of recovery is less in older patients, who often continue to have unstable equilibrium. Labyrinthine hydrops is the only one of these conditions that is sometimes reversible. In all instances, the concern of the physician and an explanation of the symptoms are of therapeutic value to the patient. The judicious use of mood-stabilizing drugs, stimulants, or other medication helps to relieve symptoms in some patients.

MESENTERIC VASCULAR OCCLUSION.

Morris, W. R. *M. Ann. District Columbia* **24:** 12 (Jan.) 1955.

The etiology, clinical features, prognosis, and treatment of mesenteric vascular occlusion are presented, along with detailed reports of 2 successfully treated cases. Nineteen cases of mesenteric vascular occlusion occurred at Doctors Hospital (Washington, D. C.) during a thirteen-year period. The diagnosis was established at operation in 7 patients and at necropsy in 4. The operative rate was 63.6 per cent and the mortality rate 42.8 per cent. In treatment, the following are emphasized: early diagnosis; immediate surgical intervention after a tentative diagnosis; rapid and adequate removal of damaged bowel, unless there is conclusive evidence of its viability; the use of blood transfusions, and especially of intra-arterial transfusions, when indicated; continuous gastrointestinal decompression and supportive parenteral therapy postoperatively; the use of an antispasmodic agent and antibiotics; and the importance of operation even in apparently hopeless cases. With such a program, the mortality rate should be reduced.

CEREBRAL HEMODYNAMICS IN PATIENTS WITH HEART FAILURE ASSOCIATED WITH HYPERTENSION AND THE RESPONSE TO TREATMENT

Moyer, J. H.; Miller, S. I., and Snyder, H. *J. Clin. Invest.* **34:** 121 (Jan.) 1955.

Cerebral blood flow and cerebral oxygen consumption were not altered in 20 patients with hypertension associated with heart failure. Treatment for heart failure did not alter cerebral blood flow or cerebral oxygen consumption in these patients. Rapid digitalization with

strophanthin K did not alter cerebral hemodynamics. Cerebral blood flow was depressed in 6 patients with heart failure associated with aortic insufficiency or mitral stenosis.

THE CHANGING ELECTROCARDIOGRAM IN WILSON BLOCK.

Papp, C., and Smith, K. S. *Circulation* **11:** 53 (Jan.) 1955.

The significance of the Wilson variety of right bundle-branch block was investigated on the basis of serial electrocardiographic changes seen in almost half of the 53 patients. Wilson block may originate from both anteroseptal and posterior infarction; in the former it may form a solitary relic without prognostic significance; in the latter it denotes extensive septal involvement. It may modify the injury pattern of anterior infarction and may abolish the signs of posterior infarction; cardiac infarction may approximate it to the classic form of right bundle-branch block. Except in 2 patients, less than 4 per cent of the series, it was related to pathologic causes; it should therefore be regarded as a sign of organic heart disease. (Authors' summary.)

ATROPHY OF AURICULAR AND NASAL CARTILAGES FOLLOWING ADMINISTRATION OF CHORIONIC GONADOTROPHINS IN A CASE OF ARTHRITIS MUTILANS WITH THE SICCA SYNDROME

Rogers, F. B., and Lansbury, J. *Am. J. M. Sc.* **229:** 55 (Jan.) 1955.

The twenty-eighth recorded case of arthritis mutilans is described. Unusual features were the coexistence of the sicca syndrome and an exacerbation of the joint manifestations together with severe destruction of the cartilages of the ears and nose following injections of chorionic gonadotrophin. This exacerbation and cartilaginous destruction suggested that an excess of gonadotrophins may be a factor in the pathogenesis of arthritis mutilans and of certain types of degenerative joint disease.

OBJECTIVE EVALUATION OF CORONARY VASODILATOR DRUGS.

Russek, H. I.; Zohman, B. L., and Dorset, V. J. *Am. J. Sc.* **229:** 46 (Jan.) 1955.

Sixteen vasodilatory drugs were evaluated by recording and comparing their specific effects on the electrocardiographic response to standard exercise in carefully selected patients with coronary disease. The following conclusions were reached: 1) Glyceryl trinitrate (nitroglycerin) in therapeutic doses exerted a strikingly favorable effect on the response to exercise as recorded electrocardiographically. This response was obtained with sublingual administration. Glyceryl trinitrate is the drug of choice for the treatment of acute attacks and for prophylaxis prior to exertion. 2) From 1 to 2 gr. of papaverine intravenously, or 3 to 8 gr. orally, decreased or abolished the abnormal electrocardiographic response to standard exercise. Such benefit was not apparent with usual therapeutic doses. 3) Peritrate (pentaerythritol tetranitrate), in a dose of 10 to 20 mg. orally, afforded protection for four to five hours in the majority of patients tested. It is the most effective drug available for prolonged prophylactic therapy in angina pectoris. 4) Nitroglyn (glyceryl trinitrate in specially coated granules designed in an attempt to permit slow absorption for prolonged action) gave poor results. A dosage as high as 4/25 gr. was associated with only slight to moderate improvement in exercise response in approximately half the patients tested and none in the remainder. 5) Metamine (trinitrate biphosphate) exerted little or no effect. 6) Paveril (dioxyline phosphate) had no striking effect, even with massive dosage. It sometimes improved exercise response but its action was transitory. 7) Ethyl alcohol (1 to 2 oz.) and morphine each failed to influence the exercise response, although they prevented or reduced the severity of anginal pain. Ethyl alcohol should be prescribed as a sedative and not as a coronary vasodilator. 8) Aminophylline, Roniacol (β-pyridylcarbinol tartrate), Priscoline (tolazoline hydrochloride), tetraethylammonium chloride, octyl nitrite, visammin (khellin), heparin, and Dicumarol (bishydroxycoumarin) proved ineffective. Only glyceryl trinitrate, papaverine, and Peritrate appear worthy of continued use as vasodilators in the management of angina pectoris.

EFFECT OF CORTISONE IN THE LONG-TERM TREATMENT OF RHEUMATOID ARTHRITIS. OBSERVATION OF THIRTY-FIVE PATIENTS OVER A THREE-YEAR PERIOD.
Towne, E. C., Jr., and Irby, R. *Am. J. Med.* **18:** 41 (Jan.) 1955.

At the end of three years, 11 patients, or approximately one third of an original group of 35 with rheumatoid arthritis treated with cortisone, had benefited sufficiently to continue the drug. Seven showed major, and 4 minor improvement. At twelve months, 19 patients were judged to have been benefited, and at twenty-four months, 13 patients. Cortisone was discontinued in the various patients because it failed to control symptoms or because of the development of toxic reactions. The severe side reactions and the respective numbers of patients affected were: psychosis, 3; edema, 3; leukopenia, 1; exophthalmos, 1; gastrointestinal bleeding, 1; and hypertension, 1. Five deaths occurred; 4 were probably directly or indirectly the result of cortisone administration. Death in 1 instance occurred twenty months after discontinuation of the steroid. The incidence of death may have been greatly influenced by the duration of the disease and the physical condition and age of the patients. Hypertension occurred in 1 other patient, peptic ulcer symptoms in 2, abscess in 6, and rapidly progressive joint damage in 2. Neither these nor numerous minor side actions caused discontinuance of the drug. Miscellaneous conditions, such as fracture of the hip and retinal vein thrombosis, occurred during treatment, but were not due to it, and required proper evaluation. The usefulness of cortisone in the maintenance management of rheumatoid arthritis is concluded to be definite but limited. Cortisone should not be used routinely but only after other measures have been given adequate trial.

DIAGNOSTIC SIGNIFICANCE OF PULMONARY HYPERTROPHIC OSTEOARTHROPATHY.
Vogel, A.; Blumenfeld, S., and Gutner, L. B. *Am. J. Med.* **18:** 51 (Jan.) 1955.

Seven case reports illustrate the classic features of pulmonary hypertrophic osteoarthropathy: 1) bone pain, aggravated by lowering of the extremities, 2) stiffness of the fingers, 3) muscular weakness, 4) broadening or cylindrical appearance of the distal thirds of the extremities due to a firm, hardly-pitting edema, 5) redness, glistening, warmth and perspiration of the skin of the affected regions, 6) intense tenderness to pressure over the affected bones and pain on passive motion of adjacent joints, and 7) progressive clubbing and dusky discoloration of the tips of the fingers and toes. Radiologically, these 7 patients showed fairly symmetrical, coarse, or lamellar subperiosteal bone formation along the diaphyses of the long bones, including the metatarsals, metacarpals and proximal phalanges. This disease may be difficult to distinguish from others as diverse as rheumatoid arthritis, thrombophlebitis, congestive heart failure, nutritional edema, and peripheral neuropathy. Its correct diagnosis is important because 1) it may prove distressing and be the cause of protracted suffering and is promptly cured by removal of the underlying, usually intrathoracic, pathologic process, and 2) it not only indicates the presence of serious disease of the lungs, particularly pulmonary carcinoma, but may precede the appearance of respiratory symptoms in pulmonary carcinoma and aid in its early diagnosis.